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THE MANAGEMENT OF A BLOOD BANK AT THE MASSACHUSETTS MEMORIAL HOSPITALS: THE NEW PROBLEM OF RH TYPING*

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IN 1938, the Massachusetts Memorial Hospitals established the first blood bank in Greater Boston. The great efficiency of this new procedure in providing blood for transfusions has resulted in its continued growth and development. In 1939 the use of placental blood for transfusions was reported.[1] In 1941 the methods followed in developing a blood bank in a large metropolitan hospital were given in detail[2] and a simplified citrate-dextrose blood preservative was described.[3] In this article I wish to report the further progress of this blood bank in dealing with the new developments in blood typing, with special emphasis on the importance of Rh typing of all donors and recipients in the bank.

The Transfusion Service at Massachusetts Memorial Hospitals not only concerns itself with furnishing blood and plasma but is also responsible for determining the causes of transfusion reactions. In 1941 several reactions were encountered that could not be explained. Rechecking of the bloods of the recipients and donors failed to show any agglutination. By typing for the Rh factor, however, incompatibility in the blood types between recipient and donor was demonstrated and, in some cases, abnormal agglutinins were found in the patient's serum.

During 1940 and 1941, Levine,[4] Wiener[5] and Landsteiner[6] published independently articles concerning hemolytic transfusion reactions encountered from the use of homologous blood that seemed to bear directly on our problem. Their conclusions are familiar and will not be dwelt on in any detail, since a complete review of the subject has recently been published by Diamond[7] and by Hooker.[8] Levine[4] pointed out that a fatal transfusion reaction may result from the use of apparently compatible blood without any previous warning. He showed that Rh− patients are immunized or sensitized to the Rh blood factor by gestation involving one or two Rh+ infants. Levine[4] believed that the patient is immunized against an antigen unrelated to the blood properties A and B, which is present in the blood of the fetus but lacking in the patient's own blood. The fetus inherits the factor from the father, who is Rh+. The fetal red cells, being Rh+, build up antibodies in the Rh− mother, so that the first transfusion of an Rh+ blood may result in a hemolytic reaction. Since no warning of such sensitization and the development of anti-Rh agglutinins in the patient's serum can be obtained from a clinical examination or history, the situation is fraught with danger. Wiener[5] also pointed out that isoantibodies for Rh, unlike those for Types A and B, do not normally occur in human plasma, and that the initial transfusion of Rh+ blood into patients who do not have isoantibodies for this agglutinogen is ordinarily uneventful, the transfused cells surviving and functioning in the circulation for as long as three or four months. Subsequent transfusions of Rh+ blood, however, result in increasingly severe reactions.

Realizing that a well-organized blood bank should safeguard its patients from the possibility of such reactions, we felt obligated to carry out Rh typing in an efficient and active manner. In April, 1942, therefore, the Massachusetts Memorial Hospitals became a sponsor and member of the Blood Grouping Laboratory, an organization formed for the purpose of, and equipped for, typing for the Rh factor in human blood.

Record of Reactions

During the past year 1169 flasks of blood have been collected and 1022 transfusions have been given. The percentage of reactions encountered was 6.4 per cent. The reactions are graded as follows: mild febrile reactions (99 to 101° F.) lasting but a short time following transfusion, with or without chills; febrile reactions (102 to 103° F.), with chills but without evidence of hemolysis; and

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hemolytic reactions, with chills and possible hemoglobinuria and jaundice. Since the formation of the blood bank in 1938, no death has occurred that could be attributed to a transfusion.

Subsequent to 1941 more than two thousand Rh determinations have been made, and over seventy-five investigations for abnormal agglutinins have been carried out on patients with suspicious reactions of incompatibility. Included in this group are transfusion reactions of mothers of infants with erythroblastosis fetalis. Of these Rh tests, 13.3 per cent were carried out on Rh− and 86.7 per cent on Rh+ persons, these figures bearing out the previously accepted statistics on the incidence of these groups in the white population. Of the patients in whom anti-Rh agglutinins were sought, 36.8 per cent gave a positive result. This likewise bears out other investigators who have found that less than 50 per cent of patients having transfusion reactions and mothers of erythroblastotic babies have demonstrable agglutinins in their blood.

Clinical Aspects

The clinical aspects of Rh incompatibility with which one is concerned are as follows: hemolytic transfusion reactions of increasing severity occurring in Rh− recipients when given Rh+ blood (such reactions may become sufficiently severe to result not only in anemia and jaundice but in anuria); serious and even fatal hemolytic transfusion reactions resulting from the first transfusion in Rh− women who have been sensitized and have developed anti-Rh agglutinins through pregnancies; and hemolytic anemia of the newborn or erythroblastosis fetalis, occurring in Rh+ infants of mothers who have developed sensitivity to the Rh factor (the severer forms of this condition result in late fetal death from congenital hydrops and neonatal death from icterus gravis).

Rules for Typing

With these indications in mind, the following rules regarding typing for the Rh factor have been made: All surgical and medical patients admitted to the hospital who have any likelihood of receiving repeated transfusions are routinely typed for the Rh factor. All patients who give a history of reactions on previous transfusions, even at a remote date, are studied for the Rh factor. All patients who require an emergency transfusion when the time element has prevented an Rh determination are checked for this factor before the second transfusion. All obstetric patients are typed before admittance to the hospital, and no surgical delivery is undertaken until the patient has been so typed. Lastly, all babies born with jaundice and anemia are typed for the Rh factor in order that their recovery may be facilitated by transfusion with Rh− blood.

Obstetric Aspects

In view of the fact that the margin of safety is much less in obstetric cases than in others, all such patients admitted through the Prenatal Service are typed for the Rh factor by at least the fifth month. The data regarding this typing are incorporated in the patient's record, so that at a later date when the patient is admitted to the hospital an improper transfusion will not be given. It is the practice of the bank to request the husband of the expectant mother to donate a pint of blood approximately two months before the mother is admitted to the hospital. The father's blood establishes a credit in the blood bank so that if an emergency arises, blood will be accessible.

Far more obstacles have been encountered with the private-ward obstetric cases than with the public-ward cases just mentioned. Far too many patients have been admitted to the hospital without previous typing, and a transfusion has often become necessary as an emergency measure. This necessitates sending the blood to the laboratory immediately, frequently during the night. To obviate this extra work, it is now required that the private patients have their blood sent to the laboratory routinely before being admitted for delivery. This rule has become necessary because of a feeling of moral and legal responsibility to prevent untoward reactions in this group of patients. Members of the obstetric staff have sufficient sterilized blood-collecting tubes and requisition blanks in their offices. They are given the choice of collecting this blood and forwarding it by mail to the laboratory or of bringing it to the hospital and having it forwarded through hospital channels. The obstetrician responsible for the forwarding of the blood is billed directly each month by the laboratory, in this way reducing the work of the hospital cashier.

For routine determinations all samples are collected by 1 p.m. and forwarded to the Blood Grouping Laboratory. Approximately 5 cc. of the blood to be examined is placed in a sterile test tube. The reports on the typing, including the Rh factor and the major grouping, are returned routinely to the hospital the following day. If, however, results of the typing are needed before that time, they may be secured by telephoning the laboratory in the late afternoon. Through these methods the number of emergency examinations has been reduced. Emergency typing can, however, be secured at any time of the day or night.

Requisitions

It is essential that sufficient data be furnished on the requisitions that accompany the samples of blood. At times it is difficult to secure these data. This has resulted in formulating the rule that prohibits a sample of blood being sent to the laboratory

unless the required data accompany it. This information is filled in on a special requisition blank. On the blanks there is requested a brief history of the case pertinent to the Rh factor. The information sought includes the reason for the examination; whether the patient is a maternity case, and if so, what the month of pregnancy is; whether the patient has had previous transfusions, and if so, whether there were reactions; whether there is a history of stillbirths, miscarriages or jaundiced babies; whether the patient had transfusions without the expected subsequent rise in hemoglobin or red-cell count; and whether erythroblastosis fetalis is suspected.

The Donor List

As the staff members became conscious of the importance of the Rh factor, the next problem to be confronted was that of securing donors. This has been solved in the following manner: All bloods collected in the blood bank are typed for the Rh factor. This is essential inasmuch as difficulties may be encountered if an Rh+ blood is given to an Rh− patient. The bloods collected are not liberated for transfusion until this typing has been reported from the laboratory. Under this method it is not uncommon to pick up routinely a sufficient number of Rh− bloods, especially in Group O, also known as the "universal-donor group," to fulfill one's needs. With this routine checking of all bloods passing through the bank it has also been possible to build up a satisfactory donor list. When it is determined that a certain donor is Rh−, the secretarial staff sends him a letter. This letter explains that his blood is of a special type and is extremely necessary in certain types of transfusions. It requests him to serve as a professional donor should an emergency arise, and informs him that he will receive the usual professional-donor fee if called on to give blood.

An attempt has been made to build up this list with the geographic location of the donors in mind. The majority of the donors on the list live in the vicinity of the hospital. On the other hand, names have been added from different communities outside of the city to aid in the securing of donors for the suburban hospitals. Similar donor lists have been prepared by the other hospitals that sponsor the Blood Grouping Laboratory. Donors on the lists may be used by other participating hospitals without expense to the recipient other than the transfusion fee. These lists are available to all physicians and hospitals. For all but indigent cases, a small fee is charged by the Blood Grouping Laboratory for furnishing the service of the donor. It has been found that this donor list is far superior to one of students, since a student list is continually changing.

There are at present 75 donors on the list at the Massachusetts Memorial Hospitals. Although it is the practice to give patients blood from donors of a corresponding blood group, it is at times necessary to use Rh− donors from Group O. It is interesting to note how closely the percentages of the four major groups follow the figures compiled by Snyder[9] based on 20,000 samples from the population of the United States. The figures are compared in Table 1.

TABLE 1. *Blood Group Percentages.*

Blood Group	Snyder	Blood Bank
	%	%
O	45	45
AB	4	4
A	41	39
B	10	12

Whenever an Rh− patient is encountered, samples are secured from other members of the family. Frequently there result several Rh− donors in the same family group.

Typing Serum

Another feature of the blood bank concerning the Rh− factor is its obligation to secure high-titer nonspecific anti-Rh serum. The staff members have been instructed to co-operate by obtaining samples of blood from their Rh− patients who have had babies with erythroblastosis fetalis. If a serum of high titer is found, the patient is encouraged, through the doctor's co-operation, to furnish blood to the laboratory for the preparation of Rh-typing serum. Many patients are anxious to furnish their blood for this cause without charge; others are given the customary donor fee.

Case Reports

The following case, encountered during the past year, is reported to demonstrate the value of routine Rh typing in the prenatal stage as an aid in prompt treatment of infants with erythroblastosis fetalis. By this routine typing a high titer of Rh agglutinins was discovered, indicating the need for early termination of pregnancy.

CASE 1. O. M., a 34-year-old woman, was admitted to the hospital on February 18, 1943, through the Prenatal Clinic, in the 8th month of pregnancy. She had had a normal pregnancy in 1941. She proved to belong to Group A and to be Rh−. The father belonged to Group O and was Rh+. The anti-Rh determination just prior to admission revealed a high titer of agglutinin. The patient was admitted because of the danger of an erythroblastotic baby. Labor was induced on February 21. The baby weighed 5¼ pounds and was slightly jaundiced with a red-cell count of 2,900,000, and a hemoglobin of 86 per cent. It was given an immediate transfusion of Rh− blood, and the anemia progressively improved. By March 6 the red-cell count had reached 4,900,000 and the hemoglobin 100 per cent. The baby was still slightly jaundiced but was improving at discharge on March 22. The mother had seven anti-Rh determinations between February 16 and March 15. An anti-Rh titer just before labor was of the same intensity as before admission. The titer fell slightly 9 hours following delivery, but the next day it reached its former higher level, and remained there for the following month. Blood from the baby's cord was Rh+ and showed a small amount of anti-Rh agglutinin. The patient was discharged from the hospital on March 3, with no complaints.

The next case is reported to emphasize the difficulties that may be encountered from incomplete typing. The Blood Grouping Laboratory, as already stated, was organized in April, 1942; this patient was admitted only a few days following that date. The value of Rh typing was not yet fully realized, which accounts for the following history and did more to educate the staff than any number of lectures would have done.

CASE 2. H. M., a 33-year-old woman, was admitted with the following past history of pregnancies: a 7-pound term baby in 1932; a 2-month miscarriage, with no known cause, in 1933; a 7¼ pound normal baby at 9 months in 1935; 3½-month miscarriage in 1936 and 1937; a 6-pound premature baby, which was alive at birth but later died of anemia, in 1939; and an 8-pound normal baby at 9 months in 1940.

During March, 1942, the patient reported to the Prenatal Clinic. The hemoglobin was 48 per cent and the red-cell count 4,000,000. She returned to the clinic on May 8 with a hemoglobin of 36 per cent and a red-cell count of 3,000,000. Because of this progressive anemia, she was admitted to the hospital for transfusion. She was reported as Type B and was transfused the following day with Type B blood from the blood bank, cross matching showing apparent compatibility. She immediately had a transfusion reaction, with a chill and fever. Soon after the reaction started, hemoglobinuria was noted and the patient developed jaundice. Sodium bicarbonate was administered intravenously. The original blood specimens were rechecked and were found by the usual technic to be still compatible. On May 9, the patient was found to be Rh−. Her husband was found to be Rh+. On May 10 the patient went into labor and delivered a small live baby whose size corresponded to that of an 8-month fetus. The baby developed anemia on the 4th day and was found to be Rh+, showing a slight amount of anti-Rh agglutinin. After transfusion the baby did well, and on discharge from the hospital it was gaining weight and the jaundice was clearing. The mother was given a transfusion of Rh− blood, without reaction. Her blood continually improved and she was discharged on May 23. Four anti-Rh determinations were made between May 19 and May 23. Immediately following the reaction the titer became markedly reduced, only to return to approximately its original strength on discharge. Later it subsided.

On March 29, 1943, the mother was again admitted to the hospital for surgery. Following operation it was necessary to transfuse her, and she was given Rh− blood, without reaction. The anti-Rh agglutinins present before this last transfusion completely disappeared.

The last case is reported simply to show the value of routine Rh determinations on all surgical cases that have a probability of repeated transfusions. If this patient had been unfortunate enough to have received Rh+ blood, he might have had a serious reaction with the third or fourth transfusion.

CASE 3. F. B., a 75-year-old man, was admitted to the Surgical Service on November 11, 1942, with a diagnosis of carcinoma of the stomach and prepared for a subtotal gastrectomy. Realizing that several transfusions might be required, the surgical staff had him typed and found him to belong to Group A and to be Rh−. He was given one preoperative transfusion and three postoperative transfusions with Rh− blood, without reaction.

SUMMARY

The methods employed by the Massachusetts Memorial Hospitals in dealing with the Rh factor in conjunction with its blood bank have been described.

To avoid hemolytic transfusion reactions and other untoward effects from the use of banked blood, it is pointed out that Rh typing is indicated for all surgical and medical patients when there is likelihood of repeated transfusions; for all patients with a history of previous reactions; for all patients who have received emergency transfusions without typing, before a second transfusion is given; for all obstetric cases, before admission, and all surgical deliveries; and for all babies born with jaundice and anemia.

It has been demonstrated that a practical and efficient method of carrying out Rh typing for all needed cases, especially in a hospital having an active obstetric service, is the organization of a blood-grouping laboratory, jointly sponsored by several institutions.

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REFERENCES

1. Barton, F. E., and Hearne, T. M. Use of placental blood for transfusion. *J. A. M. A.* **113**:1475-1478, 1939.
2. Barton, F. E. Management of blood bank at Massachusetts Memorial Hospitals. *New Eng. J. Med.* **225**:176-179, 1941.
3. *Idem.* Simplified citrate-dextrose blood preservative. *J. A. M. A.* **116**:1196, 1941.
4. Levine, P. Role of iso-immunization in transfusion accidents in pregnancy and in erythroblastosis fetalis. *Am. J. Obst. & Gynec.* **42**: 165, 1941.
5. Wiener, A. S. Hemolytic reactions following transfusions of blood of homologous group: II. Further observations on role of property Rh, particularly in cases without demonstrable isoantibodies. *Arch. Path.* **32**:227-250, 1941.
6. Landsteiner, K., and Wiener, A. S. Agglutinable factor in human blood recognized by immune sera for Rhesus blood. *Proc. Soc. Exper. Biol. & Med.* **43**:223, 1940.
7. Diamond, L. K. Hemolytic transfusion reactions due to Rh factor: preventable danger. *New Eng. J. Med.* **227**:857-862, 1942.
8. Hooker, S. B. Isoimmunization in relation to intragroup hemolytic transfusion reactions. *New Eng. J. Med.* **225**:871-877, 1941.
9. Snyder, L. H. *Blood Grouping in Relation to Clinical and Legal Medicine.* 153 pp. Baltimore: Williams & Wilkins Company, 1929.

FUNCTIONAL VOMITING AS INTERPRETED BY AUSCULTATION OF THE ABDOMEN

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THE two types of vomiting, postoperative and periodic, discussed in this article rest on a functional basis. Both are frequently the result of spasm of the pylorus, with simultaneous relaxation of the fundus and inhibition of the cardia. These factors may be produced by a number of different causes, the most important being certain drugs and the condition of the nervous system. Fatigue, alcohol and dietary excesses also play a leading part.

Many physicians and surgeons fail to remember that spasm of the pylorus is the primary cause of vomiting in these functional conditions, and that acidosis and loss of fluids are the result and not the cause. Furthermore, the antispasmodic action of luminal sodium is not sufficiently appreciated, and one frequently overlooks the fact that this drug stops vomiting in the majority of such cases, usually within half an hour. No good results are obtained by giving it by mouth, since it either is vomited or fails to be absorbed. It must be given hypodermically and in fairly large doses, the first one being 5 or 6 gr. Usually one dose is enough.

If one makes a practice of listening to the abdomen of patients with functional vomiting, one finds that they are uniformly silent before any medication is given. The spasm at the pylorus seems to effect the motility of the entire bowel. Twenty minutes to half an hour after the administration of luminal sodium peristalsis begins, and almost immediately the nausea and vomiting cease.

Postoperative Vomiting

Postoperative vomiting is of frequent occurrence. It not only may be exceedingly distressing to the patient but at times results in disaster, so far as the operation is concerned. It is more frequent in nervous, high-strung persons than in others. Its occurrence depends to a large extent on the preoperative sedative and the kind of anesthetic used. Morphine is the sedative preferred by most surgeons and the one most conducive to vomiting by its central emetic action. Many surgeons still do not realize that morphine causes, on the one hand, pyloric spasm and, on the other, hypermotility of the small intestine. The net result is an irritable bowel, which together with the shock of the operation frequently produces postoperative vomiting. If luminal sodium were always used in large doses, both preoperatively and postoperatively, the incidence of vomiting and gas pains would be reduced to a minimum. Contrary to the prevailing belief, gas pains are due to a collection of gas not in a dilated, flaccid bowel but in a hypertonic and spastic small intestine. Morphine and other stimulants of the motor function of the bowel, although they may produce a temporary relief, in the end aggravate and prolong the trouble.

Illustrative of the type of case under discussion is the following.

A 50-year-old woman had a hysterectomy and vaginal repair and was given ¼ gr. of morphine preoperatively. The anesthetic was ether. The operation was uneventful. After coming out of the anesthetic the patient vomited and continued to do so for the next 24 hours. During that time, 3000 cc. of 5 per cent glucose solution was administered intravenously and ½ gr. of pantopon was given at 4-hour intervals, but the nausea and vomiting continued unabated. Oxygen was administered, but it had only a temporary beneficial effect. On the evening of the day following the operation, I was called to see the patient. Except for the intense nausea and vomiting, she seemed to be in good condition. The temperature, pulse and respirations were practically normal. The abdomen was not distended and was completely silent on auscultation.

With the permission of the surgeon who had performed the operation, 5 gr. of luminal sodium was given intramuscularly. No other medication was administered. Twenty minutes later the first peristaltic sounds were heard, and 5 minutes after that the patient felt better. The nausea stopped and there was no further vomiting. One half-hour following the administration of the luminal sodium she asked for something to eat.

There is nothing unusual about this case, except that the nausea and vomiting were intense and prolonged. Countless other similar cases are due to the same causes — the shock of the operation, the anesthetic and the administration of morphine or pantopon or any one of these. Having listened to the abdomen of many such patients, I believe that the chief cause is a spasm of the pylorus, which permits no gas or contents to pass from the stomach into the intestine. The evidence for this point of view is that no peristaltic sounds are heard so long as nausea and vomiting persist, and that after the administration of luminal sodium, usually twenty minutes, peristaltic sounds are heard and nausea and vomiting disappear.

Periodic Vomiting

Periodic vomiting is a frequent condition during the first decade of life, especially in nervous, high-strung children. Adults, especially neurotic women, are also subject to it. It is in all probability a functional condition. It may or may not be associated with attacks of migraine and it may come at regular or irregular intervals. There is apt to be more regularity in the periodic vomiting of children than in that of adults.

The apparent cause of periodic vomiting is a neurotic background. The attacks, which are often precipitated by nervous tension, emotional upsets, fatigue and indiscretions in diet and overindulgence in alcohol, may last for a few hours or for days; indeed, in one of my cases the attack lasted for a week.

The onset is usually without much warning, often following a hard day's work or an emotional crisis. The vomiting is apt to be frequent and severe. If the stomach contents have been expelled and the stomach has been at rest for a while, any attempt to take solids or fluids is almost sure to precipitate another attack. It is useless to give medicine by mouth in these cases, since it is never retained.

Except for the abdomen, the physical examination is usually negative. The abdomen is slightly spastic and somewhat tender, owing to strain on the abdominal muscles. It is silent on auscultation and may remain so for long periods except for an occasional tinkle. There is in all probability an intense spasm of the pylorus that is transmitted over the entire length of the small intestine. So long as the spasm lasts, the vomiting continues.

The treatment for this condition varies a good deal. Excellent results have been obtained with luminal sodium given hypodermically. As much as 6 to 10 gr. every twenty-four hours may be given. It may be necessary to repeat this dosage in the second twenty-four hours, but in my experience only one patient, whose case is discussed below, failed to respond within twenty-four hours. Luminal sodium relieves spasm and slows the peristaltic rate. The following case illustrates the condition and its treatment.

A 35-year-old woman, the mother of two children, began to have attacks of periodic vomiting when she was 20 years of age, after the first child was born. For 15 years she averaged about three attacks a year, each in her opinion due to fatigue or an emotional upset. She had had repeated examinations, including several series of x-ray examinations of the stomach and intestinal tract. Nothing abnormal was found. When the attacks first began, they were extremely severe and lasted from 1 to 2 weeks. At the beginning, vomiting was frequent, occurring every half-hour or every hour, and the patient was unable to retain anything. When she attempted to take fluids of any kind, they were immediately vomited.

The last attack of vomiting occurred in October, 1941. The patient had been working hard and was extremely tired before it started. It began with the same intensity as had the other attacks. When I was called, she had been vomiting continually for 24 hours, and even turning over in bed caused vomiting. Treatment during previous attacks had consisted of gastric lavage, the intravenous administration of 5 per cent glucose solution and the hypodermic injection of a solution consisting of hyoscine, morphine and extract of cactus. On the patient's request this treatment was continued, although it was not thought that the hypodermic injections were indicated. For 3 days, no beneficial results accrued. The vomiting continued unabated, and the patient rapidly lost weight and strength.

On the 4th day, large doses of luminal sodium were given subcutaneously — 4 gr. every 6 hours. This was kept up for 2 days. On the 2nd day of this treatment, the patient still vomited, but at less frequent intervals, and the return of peristalsis was noted. On the following day, — the 6th day of the attack, — she was much improved. Vomiting stopped and she was able to take fluids without nausea. Thereafter she continued to improve.

For the past 22 months, the patient has been in good health. She has been taking two ½-gr. tablets of luminal sodium twice a week to allay the irritability of the stomach and nervous system and to prevent a recurrence of the attacks.

Only 6 cases of cyclic vomiting in children have been studied, but these were so similar in their history, symptomatology, physical findings and response to treatment that one may be hopeful that the underlying principle in these cases will hold true in a much larger group. All 6 children were between the ages of three and eight years at the time they were seen. All were nervous, and at least one parent of each child gave evidence of nervous instability. The parents of one patient were heavy drinkers and had been for several years preceding its birth. The symptomatology was much alike in all the cases, with vomiting once or twice a month and sometimes oftener, usually precipitated by fatigue, nervous tantrums or the consumption of indigestible food. Every patient was below normal weight. During prolonged attacks, acetone was present in the urine. Marked and persistent hypermotility of the bowel was the physical finding common to all cases. One of these patients, a boy four years of age, did not improve under treatment, and it was not until a pair of large, diseased tonsils had been removed that he began to do so. For the last two years his vomiting has practically ceased.

The following case is quite typical.

A 6-year-old girl had never been in good health, and her mother could not remember when she did not have periodic attacks of vomiting. When first seen, she was a pale and asthenic child and 11 pounds underweight. She had had an attack of vomiting about once a month, occasionally at shorter intervals, that lasted about three days; each caused extreme weakness and required 2 days' rest in bed to regain strength. Physical examination was normal except for evidence of extremely active peristalsis. For the previous 3 years, the patient had been under the care of a New York pediatrician, who had unsuccessfully tried many diets.

She was first seen during an attack of vomiting. One grain of luminal sodium was given intramuscularly, and thereafter about ⅓ gr. of luminal sodium was given by mouth three times a day for 3 days. The dose was then reduced to ¼ gr. This was continued for a week and at intervals during the next 6 months. On only a few occasions since then has she had any of the drug. She has now had no attacks for 3 years, except one following "grippe." Up to a year ago, she had gained 15 pounds in weight, was going to school, played games and was apparently a normal child.

Summary

Functional postoperative vomiting and periodic vomiting are in all probability largely due to spasm of the pylorus. So long as the vomiting continues, the abdomen remains silent. A few peristaltic sounds are sometimes heard at intervals.

Luminal sodium given hypodermically in large doses relieves the spasm and almost always stops vomiting. Peristaltic sounds are usually heard within half an hour after its first administration.

PRACTICAL DETAILS IN THE MANAGEMENT OF STERILITY, WITH SPECIAL REFERENCE TO ENDOCRINE FACTORS*

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THE emotional tension of wartime and the accompanying social and economic upheavals promptly reflect themselves in outworkings of the reproductive instinct. Thus are created new and larger problems of prostitution, venereal disease and illegitimacy. Thus also new demographic trends appear, notably affecting marriage, divorce and the birth rate. In 1942 this country attained an all-time record of 3,000,000 births, the highest peak of the curve coming ten months after Pearl Harbor. At the same time there has been a great increase in the number of patients seeking the relief of barrenness. It therefore seems opportune to survey the present status of the investigation and treatment of involuntary sterility, and to define those lines of procedure that have proved to be most useful in clinical practice.

CAUSATION OF STERILITY

In order to obtain the best results in the management of sterility, one must appreciate clearly the general principles of causation, which are three in number.[1] First, clinical cases of sterility are due almost without exception to multiple causes. The average such mating presents four or five demonstrable factors of infertility. In a minority of cases some one factor predominates, in the sense that it is serious enough by itself to prevent conception. Oftener the causative mechanism is a combined action of several milder factors, each of which lowers fertility to some extent and all of which together produce a sterility that is relative rather than absolute. Second, in more than 80 per cent of cases these multiple factors are divided between the husband and the wife. Thus, it is comparatively uncommon to find that the fault lies entirely with one partner. In the aggregate, the sum totals of male and female responsibility are about equal. Third, constitutional disorders, both endocrine and nonendocrine, play a large part in the causation of human infertility. In the male they are considerably more important than are local abnormalities of the genital organs.

DIAGNOSTIC STUDY OF STERILE MATING

From what has been said about etiology, it follows that every sterility problem ought to be surveyed from four viewpoints — urologic, gynecologic, medical and endocrinologic.¶ A basic routine should be followed, with supplementary examinations made on special indication. Complete study is essential to reveal all the causative factors present and so to permit a therapeutic attack from all possible angles. Procedure on this basis has more than doubled the number of successful results obtained. It would be sadly inadequate in sterility cases to accept the first abnormality discovered as the sole and only cause, on the unwarranted assumption that other faults do not coexist.

UROLOGIC MANAGEMENT

The urologist takes a history and makes a careful examination of the male reproductive organs. In a small number of cases these steps in the investigation reveal major obstacles to fertility, such as impotence, testicular atrophy and blockade in the epididymides. Oftener the examiner discovers conditions of comparatively minor importance. The most frequent finding is chronic prostatovesiculitis. This disorder was formerly considered to be a leading cause of male sterility because of the fact that the spermatozoa, after leaving the testicles, come into contact with bacteria and pus. Our experience has been that prostatovesiculitis, like any other chronic focal infection, contributes to infertility principally by elaborating toxins that pass into the blood stream and depress spermatogenesis.

In complete azoöspermia, fortunately comparatively uncommon, it becomes necessary to distinguish between inactivity of the seminiferous tubules and bilateral obstruction of the epididymides. Puncture and aspiration of the testicle have been used to make this differential diagnosis. A better method is testicular biopsy, which gives precise information about the functional condition of the germinal epithelium. If adequate spermatogenesis is found to be going on and if spermatozoa are present in the epididymides, the operator may proceed to perform an epididymovasostomy. Although this operation succeeds in only a minority of cases, it offers the only chance of remedying an otherwise hopeless situation.

The critical examination of semen has contributed more to the successful management of sterility than has any other detail of modern progress. With cer-

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¶In 1927 we organized the first systematic group study of sterility with the invaluable collaboration of the late Dr. A. W. Rowe. The details of the diagnostic methods originally used by us are reported in previous publications.[2] During the last ten years experience has shown that certain examinations and tests can be omitted from the routine program without lessening its practical utility. Certain others have been added. In particular, new developments in endocrinology have led us to modify radically our diagnostic and therapeutic approaches in that field.

tain reservations, it may be assumed that a quantitative estimate of male fertility is afforded by the mathematical evaluation of the spermatozoa on the four counts of number, morphology, motility and endurance. An average normal specimen contains 100,000,000 spermatozoa per cubic centimeter; 80 per cent of these are mature and well formed; 75 per cent exhibit lively motility; and under favorable conditions of temperature and moisture they remain active for the better part of twenty-four hours. If a specimen falls notably short of these standards in any respect, some degree of infertility is indicated. An excess of morphologic faults is a finding of the greatest significance, since it strongly suggests a constitutional disorder. Unfortunately, only a minority of urologists make a practice of evaluating seminal morphology, and in consequence innumerable cases of male infertility go unrecognized. This point is so important that it deserves illustration.

Case 1. Mr. and Mrs. A had been married for 6 years and involuntarily sterile for 5. The wife presented no serious obstacle to fertility. The husband's semen showed a sperm count of 60,000,000, with 32 per cent abnormal forms, a motility of 70 per cent and an endurance of 10 hours. There was nothing grossly wrong with his genital organs. He was referred back to his family physician with the recommendation that he be further studied from the medical and endocrinologic viewpoints. The physician elected to send him to a urologist, a man eminent in his field but without special experience in sterility. The consultant reported that the patient was free from prostatovesiculitis, that his semen contained large numbers of active spermatozoa and that he might therefore be regarded as perfectly fertile. This opinion prevailed. The wife was subjected to a useless curettage, and is now, I believe, receiving vitamin E. She has not conceived nor, unhappily, is she likely to do so.

By way of contrast, a case is cited in which a similar problem was handled intelligently.

Case 2. Mr. and Mrs. B had been married and involuntarily sterile for 3 years. By a former marriage the husband had a son 8 years old. The referring physician reported that the wife's uterus was retroflexed and contained a fibromyoma as large as a hen's egg and that the husband's semen appeared excellent. A complete investigation of the couple was carried out. Insufflation of gas showed the tubes to be patent, and postcoital examination demonstrated that spermatozoa had reached the cervix; thus both of the uterine conditions were proved unimportant as factors of infertility. The semen had a sperm count of 72,000,000, with 34 per cent abnormal forms, a motility of 75 per cent and an endurance of 24 hours. No local genital lesion was demonstrable. Constitutional study of the husband identified chronic dental infection, poor hygiene, and mild hypothyroidism. He was treated; his wife was not. The abnormal forms diminished to 23 per cent. Two months later the wife conceived, and she is now approaching the end of an uneventful pregnancy.

Pregnancy has followed improvement in seminal morphology in so many cases that one may justifiably assume a cause-and-effect relation. A detail of Case 2 worthy of emphasis is the fact that the husband, the responsible partner in this sterile mating, had been able to produce a conception nine years previously. Individual fertility levels are not constant but undergo continual fluctuations. This is easily demonstrated in male patients, in whom conspicuous changes for the better or for the worse may occur within a few months.

Gynecologic Management

An adequate gynecologic survey of the infertile woman includes the following items: history, abdominopelvic examination, measurement of the uterine index, study of the endocervical secretions, postcoital examination, a test of tubal patency and the taking of a specimen for endometrial biopsy.

Certain details of the gynecologic history acquire special importance when the complaint is sterility. Among these are duration of marriage, use of contraception and pregnancies, if any, with their outcome. Inquiry about the sex life sometimes reveals such infrequency of intercourse that on this count alone the chances of conception would be small. Normal menstrual behavior usually means that ovulation occurs, although exceptions are not uncommon; abnormalities are worthy of close attention as possible indications of ovarian malfunction. Perhaps a third of observant women report periodic midmenstrual phenomena, such as brief spotting, leukorrhea and *Mittelschmerz*; these symptoms presumably coincide with ovulation. Information should be obtained about previous investigation and treatment for sterility, as well as about pelvic and abdominal operations of any sort. Two recent patients took treatment for years in the hope of conceiving, unaware of the fact that they had undergone bilateral salpingectomy.

Positive findings on abdominopelvic examination must be specially evaluated with regard to their effect on fertility. Many gross lesions, notably the majority of uncomplicated retrodisplacements of the uterus, are unimportant from this point of view. On the other hand, conditions ordinarily trivial sometimes become highly significant in sterility cases. Chronic Skene's adenitis indicates old gonorrhea, with the ever-present possibility of tubal occlusion. Stenosis of the external os and strictures of the cervix may prevent free drainage of the endocervical secretions. Stigmas of hypoplasia are often in evidence, particularly in the form of a cervix that is long, conical and anteflexed. Polycystic ovaries represent the result of faulty ovulation in the past and at the same time offer an impediment to normal ovulation in the future.

Some years ago, one of us (S. R. M.[3]) defined the uterine index, a quantitative measure of the differential development of the uterus based on the relative lengths of corpus and cervix. In a completely infantile uterus the index is 0.25; in the mature organ it is 0.75 or higher. True infantilism is rare, although many practitioners have the habit of making this diagnosis whenever the uterus seems small; but lesser degrees of female genital hypoplasia frequently present themselves, and are clinically important because of the fact that underdeveloped ovaries produce few if any highly fertile ova.

The endocervical mucus must afford an environment favorable to spermatozoa if they are to reach

the upper genital tract in good condition. It normally undergoes a cyclic variation in consistence, being rather thick and viscid through most of the month but becoming thinner around the time of ovulation. Congestion, inflammation and faulty drainage may lead to the formation of an inspissated mucous plug that entangles and kills the male cells. In such cases pregnancy is sometimes made possible by such simple measures as the passage of a sound, precoital clearing of the cervix and the use of heat. When the trouble is more obstinate it may require cauterization, conization with the high-frequency current or a slight plastic operation to enlarge the external os and provide freer drainage.

For postcoital examination the wife reports two hours or less after intercourse. Microscopic study of the cervical contents shows the presence or absence of spermatozoa and the condition of those present. The special value of this test lies in the information that it affords as to normal delivery and reception of the male cells. It also gives direct evidence of the favorable or harmful effect of the endocervical environment. The recovery of living spermatozoa from the cervix indicates that the husband possesses at least some degree of fertility, but does not suffice to permit the necessary quantitative evaluation. The findings of postcoital examination should always be correlated with the results of direct examination of the semen.

There are two standard methods of testing the patency of the tubes: transuterine insufflation of gas and transuterine injection of iodized oil, followed by x-ray. Each of these has its particular advantages. Insufflation gives more information about the functional condition of the tubal musculature, whereas hysterosalpingography is superior for the demonstration of structural conditions and for distinguishing unilateral from bilateral patency. It is generally good practice to do insufflation first, reserving oil injection for those cases in which the tubes are not normally patent to gas. Apparent blockades sometimes disappear when chronic passive congestion is relieved by the use of heat or when a retrodisplacement is corrected. Both insufflation and injection have therapeutic as well as diagnostic value: they are indicated in mild obstructions, in occlusions unsuitable for operation and as a detail of the aftercare of salpingostomy.

There is, unfortunately, no test that demonstrates conclusively whether ovulation has occurred. Indirect evidence may be obtained by any of half a dozen technics, of which endometrial biopsy is the most practical. By a simple office procedure a small sample of endometrium is taken not longer than three days before the beginning of a menstrual period. If the specimen shows a normal secretory phase, one may conclude that the ovary contains an active corpus luteum, presumably the result of a recently ruptured follicle. Such a finding does not, however, prove that a highly fertile ovum has been liberated. In cases in which the premenstrual endometrium fails to exhibit a physiologic secretory phase, there is strong reason to believe that the cycle just ending has been anovulatory.

The surgical treatment of female infertility includes procedures of three general sorts. Mention has been made of dilatation and of tracheloplasty for the purpose of improving drainage of the endocervical secretions. Operations to restore tubal patency may be undertaken with a fair hope of success, provided that cases are carefully chosen and that the aftercare is skillful.[4] Conservative surgery of the ovaries, notably the removal of retention cysts and persistent corpora lutea, is sometimes necessary to make ovulation possible. Two other procedures should be mentioned only to be condemned. Suspension operations are irrational unless malpositions of the uterus are complicated by conditions demonstrably unfavorable to conception; they ought never to be performed except after a therapeutic trial of reposition and use of the pessary. Curettage of the endometrium as commonly practiced is not only valueless as treatment for sterility but sometimes harmful.

There is still a widespread misconception among both physicians and laymen about the indications for artificial insemination with the semen of the patient's husband. The general impression seems to be that this is a procedure of last resort, to be tried when other methods of treatment have failed. As a matter of fact, artificial insemination offers no advantage whatever over sexual intercourse in cases where spermatozoa are naturally delivered to the cervix and there encounter a favorable medium. Its utility is therefore limited to the treatment of such comparatively uncommon disorders as hypospadias, impotence, vaginismus and intractable hostility of the endocervical mucus. On the other hand, insemination with donor semen, now coming more and more into favor, provides a remedy for childlessness in that large group of matings in which the husbands are incurably sterile.

Medical Management

Stock breeders have always found it profitable in terms of dollars and cents to pay attention to the general physical well-being of their flocks and herds. In the old days physicians made a point of giving similar care to their sterility patients. With the featuring of complicated modern technics of investigation and treatment, this simple aspect of management has become neglected. It should receive more consideration, for the proper functioning of the gonadokinetic mechanism depends in no small measure on sound health and good hygiene.

Complete study of cases brings to light a high incidence of certain constitutional factors of infertility. One of the commonest of these is poisoning from chronic focal infection of the teeth, tonsils or paranasal sinuses. Chemical poisons — for

example, lead and alcohol — fall into the same category. Debilitating diseases of all sorts are important, particularly the milder grades of anemia frequently encountered. Among dietary faults inadequate protein intake easily holds first place; avitaminosis is occasionally found. Sterility patients are often underexercised and in consequence suffer from the effects of a sluggish metabolism. Many of them, especially men, are victims of overwork, nervous tension and the general complex created by the artificial conditions of modern civilization.[5]

It is clinically demonstrable that disorders of the sorts just mentioned depress human fertility, sometimes severely. The practitioner who seeks and treats them as routine will accomplish not a few cures impossible by other means.

Endocrinologic Management

Physicians have come to believe that the results of endocrine treatment of infertility are generally disappointing. Many of the physiologic responses obtained in laboratory animals fail to manifest themselves with the same regularity in human beings. Optimistic claims made for new hormonal preparations prove to be exaggerated. Moreover, glandular therapy as commonly practiced in sterility cases can scarcely be expected to bring any great measure of success, since oftener than not it means simply the haphazard giving of "shots" on insufficient indications.

Although the efficacy of present-day endocrinologic methods admittedly leaves much to be desired, the fact remains that in certain types of cases the judicious use of potent glandular preparations increases fertility to the point where conception becomes possible. To accomplish such results the practitioner must have the best possible idea of the endocrinopathic states responsible for infertility and of the lines of procedure that offer a reasonable chance of correcting these disorders. He should also bear in mind that there are two important prerequisites to successful endocrine therapy. First, coexistent nonendocrine factors of infertility must be eliminated. Measures to stimulate the ovaries are obviously futile if the wife's tubes are closed or the husband has azoöspermia, and yet an immense amount of treatment fully as irrational as this has been administered. Second, conditions inhibiting normal endocrine function should be removed. Under this heading come local impediments to ovulation, such as retention cysts, and in both sexes any type of depressing constitutional state, particularly toxemia from chronic focal infection.

Since the chief aim of opotherapy in sterility is to improve the production of spermatozoa or ova, it is worth while to review briefly the endocrine mechanism that controls gametogenesis. Among the several hormones supplied by the anterior lobe of the pituitary gland there are two, or possibly two phases of the same hormone, that are gonadotropic or gonadokinetic in the sense that they stimulate testicular and ovarian function. In the male these hormones maintain the activity both of the seminiferous tubules and of the interstitial cells of Leydig. The interstitial cells in their turn elaborate the androgenic or male sex hormone, testosterone. In the female the pituitary gonadotropic hormones bring about cyclic ripening of follicles and formation of corpora lutea. The ovarian follicle secretes the female sex hormone, estrin; the corpus luteum produces estrin and progesterone. Both testosterone and estrin have the property of limiting or checking the secretion of gonadotropins; thus a pituitary-gonad balance is established. To a certain extent this balance is dependent on the proper functioning of other endocrine glands, notably the adrenal cortex, the islands of Langerhans and the thyroid gland.

The four endocrine disorders that figure most prominently as factors of human infertility are hypogonadotropism, male hypogonadism, female hypogonadism and hypothyroidism.

Hypogonadotropism

An insufficiency of pituitary gonadotropic action during adolescence results in some degree of genital hypoplasia, with permanent anatomic stigmas and functional impairments that can seldom be corrected after the end of the plastic age. Hypogonadotropism occurring in adult patients leads to an underfunction of the testicles or ovaries that, provided that these organs are essentially normal, often responds to treatment.

It is not easy to make a precise diagnosis of the gonadotropic insufficiencies that usually present themselves in sterility cases. In men and nonpregnant women the urinary output of the hormones in question is so small that assays are not very helpful. Blood-serum assays may be more informative. If all other causes of poor spermatogenesis can be ruled out, such findings as oligozoöspermia and defective morphology may be presumed to indicate either subnormal stimulation of the seminiferous tubules or subnormal responsiveness, both of which conditions suggest the need of a stronger gonadotropic effect. Similarly in women one arrives at a diagnosis of hypogonadotropism indirectly, on the basis of evidence of poor follicular function obtained from endometrial biopsies, pregnanediol determinations and vaginal smears. In both sexes a proper therapeutic test often serves to confirm the presumptive diagnosis.

For purposes of treatment there are available preparations of the pituitary glands of animals and anterior-pituitary-like substances of chorionic origin derived either from the urine of pregnant women or from the blood serum of pregnant mares. All these must be given parenterally, since their active principles are destroyed by trypsin. Each of them is reported to have accomplished good results in

cases of deficient spermatogenesis.[6] As to their effect on the ovaries, they have somewhat different properties. Pituitary gonadotropins tend to ripen follicles, whereas the chorionic hormones are predominantly luteinizing. For this reason it is often advisable to use these preparations in some sort of combination. Excessive dosage should be avoided, since it may produce atresic follicles and other degenerative changes.[7]

In theory, gonadotropic therapy ought to be a specific remedy in that considerable group of cases in which deficient gametogenesis is due to pituitary underfunction. In practice, results have not come up to expectations, but successes are frequent enough to warrant the use of this method when rational indications for it are present.

Male Hypogonadism

Hypogonadism in adolescent boys interferes with the development of the secondary sex characteristics. When the secretion of testosterone drops below the normal level in adult men, other results appear. There is sometimes loss of sexual desire and potency. A more constant effect is depressed functioning of the epididymides, prostate gland and seminal vesicles.

Testosterone insufficiency may be demonstrated by absence from the urine of the degradation product androsterone. The semen is likely to be reduced in volume and to exhibit increased viscosity. The most frequent spermatozoic defects in such cases are diminished motility and short duration of life, if not complete necrospermia. Other types of poor semen, notably those with oligozoöspermia and abnormal spermatozoa, are seldom if ever caused by a lack of androgenic hormones.

From the foregoing facts it follows that there are two main indications for testosterone therapy in sterility. First, androgens are valuable in impotence when this disorder is directly caused by hypogonadism. The physician should, however, bear in mind that in most cases impotence is primarily of psychic origin. Second, decreased spermatozoic vitality and thick, scanty semen indicate the need for physiologic stimulation of the epididymides and accessory glands. When androgenic treatment is undertaken it is usually advisable to give gonadotropins also, to offset the tendency of the gonadal hormones to check or inhibit the function of the anterior lobe of the pituitary gland. Without this precaution there is considerable risk of depressing spermatogenesis.

Female Hypogonadism

Inadequate secretion of estrin at the time of adolescence prevents the full development of secondary sex characteristics. In mature women a lack of estrin or progesterone, or both, produces a number of effects, in particular pathologic muscular and epithelial reactions in the tubes, uterus and vagina. The uterine disturbances may lead to abortion, as well as to various menstrual disorders, but as a factor of sterility in the sense of inability to conceive, female hypogonadism plays a relatively minor role. This endocrinopathy is a result, rather than a cause, of abnormal ovarian behavior.

Urine assays afford quantitative information concerning the excretion of the derivatives of estrin and of progesterone; in cases of the more obscure type these tests are worth the difficulty and expense entailed. Ordinarily one depends on vaginal smears to reveal estrin deficiency, and on endometrial biopsies to show insufficiency of progesterone.

The chief practical uses of estrogens in sterility, however, are not for replacement therapy in demonstrable underfunction of the ovaries, but rather for specific stimulation of the tubes and uterus. Thus, good results have been obtained in tubal obstructions, both hypoplastic and inflammatory.[8] Thus also, whenever any marked degree of genital hypoplasia is present, a course of estrogenic treatment may advantageously precede attempts to stimulate ovulation by the administration of gonadotropins.[9] For these purposes diethylstilbestrol and the various biologic preparations appear to be equally satisfactory. In no way, either as replacement or as stimulation, can ovarian therapy logically be expected to improve oögenesis. Nevertheless, by some mechanism imperfectly understood, cyclic estrin-progesterone treatment of certain menstrual derangements, notably amenorrhea and anovulatory bleeding, is not infrequently followed by conception.[10]

Hypothyroidism

It is a well-established fact that in both sexes underactivity of the thyroid gland, even of slight degree, exerts a markedly depressing effect on fertility. The mechanism may be either a secondary upset of the pituitary-gonad balance or the harmful influence of a sluggish metabolism on the germ plasm. Whatever the explanation, clinical experience proves that an adequate level of thyroid function is one of the requisites of good spermatogenesis and oögenesis.

Routine examination of infertile patients reveals a considerable incidence of hypothyroidism. Many of these patients have low metabolic rates, slow pulses and subnormal temperatures but are free from the more conspicuous signs and symptoms of their disorder. They are energetic and alert and not overweight, and in general present nothing of the typical myxedemic picture. The semen often shows oligozoöspermia or a high percentage of abnormal forms.

It should be remembered that a low metabolic rate is not by itself proof of hypothyroidism, and that treatment instituted on this sole indication may be useless or even harmful. But when the diagnosis is properly established and other factors

of infertility are ruled out, replacement therapy, with periodic checks to regulate dosage, gives remarkably satisfactory results.

Summary

Some forty or fifty abnormal conditions are now recognized as obstacles to human fertility. These include constitutional depressions as well as disorders of the reproductive organs. In the typical clinical case of involuntary sterility several of these factors are present, and they are usually divided between the husband and the wife. This paper discusses the methods of complete diagnostic study prerequisite to any well-organized plan of treatment.

References

1. Meaker, S. R., and Vose, S. N. Nature [illegible] human infertility. *J. A. M. A.* 115:1426-1428, 1940.
2. Meaker, S. R. *Human Sterility: Causation, diagnosis, and treatment.* 271 pp. Baltimore: Williams & Wilkins Company, 1934. Pp. 79-191.
3. *Idem.* Uterine index of development: definition of new diagnostic sign, together with historical note on uterine sound and description of new instrument, hysterometer. *Boston M. & S. J.* 196: 615, 1927.
4. Solomons, B. Sterility, with special reference to surgical possibilities. *Surg., Gynec. & Obst.* 60:352-362, 1935.
5. Reynolds, E., and Macomber, D. Theory and practice of relative infertility in human marriages. In *Fertility and Sterility in Human Marriages.* 285 pp. Philadelphia: W. B. Saunders Company, 1924. Pp. 166-180.
6. Lane-Roberts, C., Sharman, A., Walker, K., and Wiesner, B. P. Treatment of male sterility. In *Sterility and Impaired Fertility.* 419 pp. New York: Paul B. Hoeber, Incorporated, 1939. Pp. 160-184.
7. Greenblatt, R. B. Histologic changes in ovary following gonadotropin administration. *Am. J. Obst. & Gynec.* 42:983-996, 1941.
8. White, M. M. Effect of follicular hormone on non-patent fallopian tubes. *Brit. M. J.* 1:342-344, 1940.
9. Lane-Roberts et al. Treatment of female sterility. Pp. 294-346.
10. Hamblen, E. C. Use of female sex hormones in clinical practice. *Surg., Gynec. & Obst.* 74:490-495, 1942.

BOSTON MEDICAL LIBRARY

Report of the Librarian*

THE Library passed through its second year of our participation in the war, unbombed, unwept and almost unsung. The trustees carried their burden with fortitude; the librarian made a moderate effort to use his budget appropriately; and the director and staff continued to serve the fellows and the public in the standards so long established. Slowly, as many of our more active members, the young men and women in the full bloom of their inky careers, went into the services or were called for more arduous and time-consuming hospital or teaching jobs, attendance fell off to one third and the use of our books, periodicals and pamphlets decreased by an almost equal amount, when compared with the figures for 1942. So, too, did interlibrary loans. We were not actually hibernating, but our activities were somewhat slowed down in relation to the number of people we served daily. Within the Library itself, however, work went on at an even increasing pace. We tried to catch up on cataloguing and, although only 2000 new items were added to the Library in 1943, 15,000 catalogue cards were written, thus finally making available to our readers hundreds of volumes, not previously classified and catalogued. Much time was given, moreover, to our duplicate material, the director being only too glad to have a few extra moments for this important work. We were fortunate in receiving a considerable number of physicians' libraries as gifts during the year. This welcome material means to the director and his staff careful checking for items that we do not have, comparing all duplicates with our copy in order to retain the best and discard the old, classifying and cataloguing the new accessions and finally putting the items into circulation. Thus a personal library, donated by a physician or his heirs, is integrated into our collections. In this way our library was largely built up in the past and our shelves are filled, as you well know, with the personal books formerly owned by past members. Such is the natural growth of a library such as ours, for the deeds of good men live after them in our overflowing stacks.

The rate of use of our collections remains about the same from year to year, although the quantity is less as the war proceeds. The 6000 readers of all types in 1943 used slightly more than four items apiece. Members, however, averaged eight items per individual for home use and about fifteen for use in Holmes Hall. Such figures are of little value for meticulous analysis, since many members did not use the Library at all. The estimates go to show, however, much to the satisfaction of the librarian, that the Library is used perhaps more extensively than many of our colleagues realize.

*Read in part at the annual meeting of the Boston Medical Library, March 7, 1944. The full report will appear in the *Sixty-Eighth Annual Report of the Boston Medical Library* (Boston, 1944).

Book-Review Department

The war has caused some changes in book reviews. Fewer long reviews can be published in the *New England Journal of Medicine* owing to restrictions of space, and fewer reviewers, particularly the younger men who often were actively engaged in research and the writers of books in their specialties before the war, are available. To ease the situation, an excellent compromise has been made; as each book is received, a brief description of its contents, usually limited to six or eight lines, accompanies the listing under "Books Received." In addition, certain books are selected for more extensive critical appraisal by competent reviewers, whose names are published in each index number of the semiannual volumes of the *Journal*. In 1943, seventy-eight

physicians furnished one hundred and forty-six reviews. The quality of the work seems to the librarian to be uniformly good, for men chosen for this combined service to the *Journal* and the Library are among the outstanding members of the medical profession. The librarian, moreover, is fully convinced that their reviews are sounder because they are unsigned. So long as the quality of the group of reviewers is maintained, even the most sensitive author has little reason to complain of their unbiased and natural sentiments. The librarian has yet to see a grossly unfair or overpersonal book review in the *Journal*. He only wishes more reviewers would add punch to their blows! There are far too much slipshod writing, inconsequential changes to make a "new edition," and poor publishing in medical literature.

Occasionally a book is reviewed in the editorial columns of the *Journal*, particularly contributions of local interest or of outstanding value as distinctive additions to medical advancement. Three such books were so treated in 1943: the splendid book *The Embryological Treatises of Hieronymus Fabricius*, translated and edited by Howard B. Adelmann, of Cornell; F. C. Irving's *Safe Deliverance*, a sound history of the Boston Lying-in Hospital and the growth of obstetrics in Boston; and Nurse Redmond's *I Served on Bataan*, a stirring account of her experiences.

Special Accessions

With book funds limited to specific purposes, the addition of books in certain fields of medicine continues to be one of the main functions of the Library. To spend such funds wisely and well is not by any means an easy task, but paths well laid down by our predecessors are usually followed in the fields of incunabula, early English imprints, Americana and books in Hebrew.

Incunabula

Twelve incunabula were added in 1943, ten after the *Catalogue* was compiled. Thus the total number of incunabula of medical and scientific interest in the Library at the end of 1943 was six hundred and eighty-four, representing the most complete collection of its type in America. With the publication of Mr. Ballard's *Catalogue*, dated 1944 but not including all accessions in 1943, it is presumed that the collection will become more widely known by scholars and consequently more useful to them. The additions, moreover, in 1943 have helped to fill out certain sections of the collection, thus carrying out our aim to make the incunabula on our shelves as representative as possible, without duplicating other holdings in Boston and its immediate vicinity. Along this line it may be noted that the addition of *De urinis et pulsibus* by Aegidius Corboliensis, according to the Stillwell *Census*, brings the first copy of this book to New England. Three more books, or editions, of the prolific writer Philippus Beroaldus bring our total of volumes by this author up to eighteen. The Library has added another example of the *Lunarium* of Bernardus de Granollachs and now possesses three editions of this rare book, two in Latin and one in Italian. The *De lamiis et phitonicis mulieribus* by Molitoris is another book not previously listed as in New England. Still in line with the same policy is the acquisition of the *Expositio in libros posteriorum* by Thomas de Aquino, for by consulting Stillwell we find three other copies distributed in the United States, in San Marino, California, Chicago and Baltimore. With the addition of one in Boston, the regional distribution for scholars appears to be excellent. Finally, a book by Trithemius not previously represented in our collection is the only copy, according to Stillwell, in a library on the East Coast. Thus, in buying incunabula in 1943, the geographical availability of these rare books has been given due consideration in its proper relation to all the other factors that go into wise selection.

Mr. Ballard's *A Catalogue of the Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library*, finished by February, 1943, could not be printed until the last of the year owing to war conditions, and therefore was not published until 1944. In spite of the complicated nature of the task of compiling this book, only one important error has been noted. The illustration of a manuscript in Hebrew by Bernard of Gordon (Fig. 3, page 11) was inadvertently printed upside down. This annoying oversight is not fully accounted for, but one fact in explanation, although not excusing our carelessness, is of interest. The manuscript, formerly in the Prince Dietrichstein library, was also inserted upside down by the original binder of the volume, apparently unnoticed by the Prince's librarian! A new plate, with the illustration in correct position, has been printed and distributed to subscribers of the *Catalogue* and inserted in copies for future sale.

English Imprints before 1640

Two valuable and important imprints in this class were added in 1943: the first English surgery, *The Noble Experyence of the Vertuous Handy Warke of Surgeri*, by Hieronymus Brunschwig, printed in Southwarke by Peter Treveris in 1525, and *The Grete Herball*, issued the next year by the same printer from the same section of London. These two books, with two others previously acquired, *The Vertuose Boke of Distyllacyon* and *The Judycyall of Uryns*, bring to the Library examples of the four important folio publications of medical interest issued in the early sixteenth century in English. They serve to illustrate the character of early Tudor medicine at a time when medieval medicine was still holding sway, although beginning

to loosen its grip before the overwhelming might of the humanistic and scientific Renaissance.

Brunschwig, an Alsatian field surgeon, who wrote a detailed account of gunshot wounds, was the author of a famous work on surgery, written in the Strassburg dialect and published in Strassburg in 1497. lieve that he was a scholarly observer who drew many valid conclusions from his practical surgery on the field of battle. The striking illustration on the title page of the man being trephined for a head wound shows marked powers of observation. The right facial paralysis is well shown; it is clearly of

FIGURE 1. *The Title-Page of Brunschwig's* Surgeri (*London in Southwarke, 1525*).

The book was popular and full of striking illustrations. The English translation of Brunschwig's *Surgeri* (Fig. 1), printed in 1525, omits much of the text and many of the woodcuts, but still preserves the essence of the work with the description of ligature of vessels and reduction and immobilization of fractures. Although Jerome of Brunswick has not been awarded a high place in medical history, a careful reading of this book leads one to believe that he was a scholarly observer who drew many valid conclusions from his practical surgery on the field of battle. The striking illustration on the title page of the man being trephined for a head wound shows marked powers of observation. The right facial paralysis is well shown; it is clearly of the peripheral type, with the wide palpebral fissure and smooth brow. A third nerve palsy is shown on the other side, the eye being pulled to the outer corner by the unopposed action of the sixth nerve, with the dilated pupil, the result of unrestrained sympathetic stimulation. A paralysis of the left side of the tongue is also well shown. This drawing resulted from more than a hasty glance by the surgeon. The book, moreover, contains much good

advice to students and young surgeons and was certainly worthy of the folio volume provided by Treveris. One only wishes that the whole of the book with all the illustrations had been included in the first important surgery to appear in England.

The second book, *The Grete Herball* (Fig. 2), was translated from the French by Peter Treveris, the printer of Brunschwig's *Surgeri*, and issued from his press in Southwarke in 1526. Its predecessor, *Le grant herbier*, was one of the many fifteenth-century French herbals, dealing with medicinal plants and the virtues of herbs as remedies used in the treatment of disease. This was one of the most popular of the early herbals, compiled from sources going back into the Middle Ages. The book printed by Treveris became the most famous of the early English herbals. It was preceded in England by only one other herbal, issued by Richard Banckes in 1525, recently published in facsimile from the rare copy in the British Museum.

An important part of herbal medicine was the preparation of the herbs by distillation. To Hieronymus Brunschwig, the surgeon, we also turn for the most complete treatise of the time. This, *The Vertuose Boke of Distyllacyon* (Fig. 3), was published by Laurens Andrewe in London in 1527. It describes the elaborate apparatus used in the technical procedure of preparing herbs.

The fourth book deals with a study of urine, one of the most valuable aids to diagnosis known to the

Peter Treveris hath
The grete herball
whiche geueth parfyt knoulege and vnder
standyng of all maner of herbes ...
of all maner of sekenesses ...

FIGURE 2. *The Title-Page of* The Grete Herball (*London in Southwarke, 1526*).

sixteenth-century physician. Urinalysis was developed to such an extent that often the physician made the diagnosis without ever seeing the patient. The book was also to be used by the patient so that he could properly describe the urine to his physician.

America (Boston, 1749–1751), in two volumes, by William Douglass, the writer of the controversial pamphlets against Zabdiel Boylston, has long been a desired item. Benjamin Rush's *An Account of the Sugar Maple-tree* (Philadelphia, 1792) is a wel-

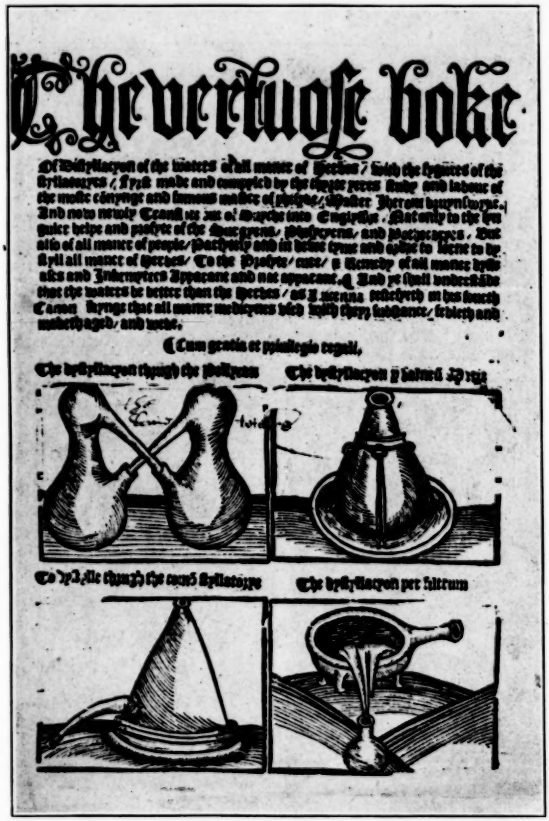

FIGURE 3. *The Title-Page of Brunschwig's* The Vertuose Boke of Distyllacyon (*London, 1527*).

The folio, *The Judycyall of Uryns* (Fig. 4), was published by Peter Treveris about 1527.

American Imprints

To the books published in this country we have added a few important items. The first edition of *A Summary, Historical and Political, of the First Planting . . . of the British Settlements in North* come addition, as is the personal copy, with corrections, of *The Young Stethoscopist* (New York, 1848) by Henry I. Bowditch. The Library, moreover, has also acquired the first issue of the *Art Anatomy* of William Rimmer, published in Boston in 1877.

Other Accessions

The Library added in 1943 the daybooks of Silas Brown, of North Wilmington (1809–1844); the

prescription books from Lemon Drug Store, Marblehead (1830–1870); a considerable collection of various foreign imprints, including Linacre's translation of Galen's *De pulsuum usu*; many medical dissertations from the College of Physicians, Philadelphia, and the University of Rochester; and numerous other gifts or purchases.

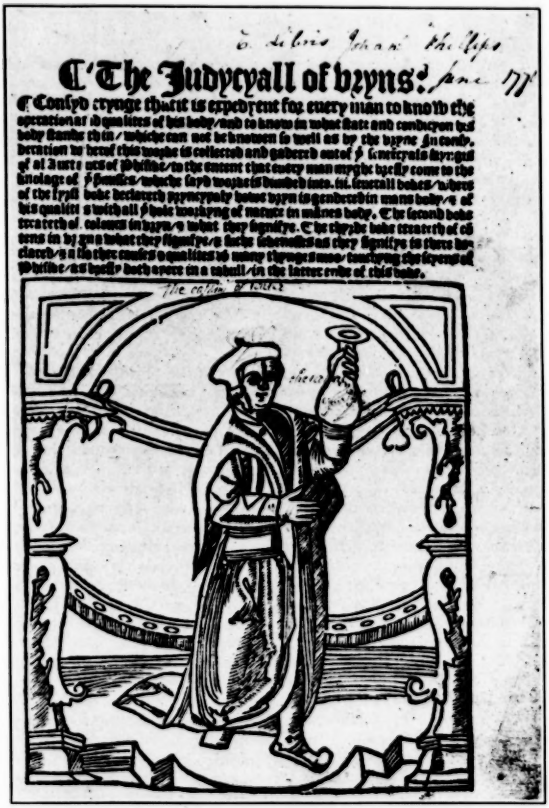

FIGURE 4. *The Title-Page of* The Judycyall of Uryns (*London, 1527?*).

* * *

The Library continues to enjoy its close association with *The New England Journal of Medicine* and *The Journal of Bone and Joint Surgery*, both quartered in our building. In addition, a rearrangement of space has allowed for a further expansion of the ever-increasing activities of the Massachusetts Medical Society, long a close associate and ardent supporter of the Boston Medical Library. With these friends and others, together with the loyal work of the trustees and the various committees, the librarian looks back on 1943 as a successful year in medical library history and toward a fuller stage of usefulness to the medical profession and to the public in the years to come.

HENRY R. VIETS, *Librarian*

MEDICAL PROGRESS

LIVER INTOXICATION

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INTEREST in the variou factors, toxics and infectious, affecting hepatic function has increased rapidly in recent years. Particular impetus has been given to clinical observations and physiologic studies of hepatic disturbances because of the prevalence of various types of hepatic disorders incident to wartime activity, both those associated with war production and those encountered in the armed services.

The role of specific toxins capable of producing liver damage is reasonably well known, and the variety of substances that may become operative under various conditions is well summarized in an article by Ottenberg and Spiegel.[1] This article reviews the causative agents, pathogenesis, interrelations and clinical characteristics of nonobstructive jaundice due to infectious and chemical agents. Special discussion is devoted to the direct and indirect effects on the liver of the following chemical substances: arsenates, phosphorus, manganese, gold, antimony, selenium, alcohol, chloroform, avertin, carbon tetrachloride, acriflavine, dinitrophenol, synthalin tetrachlorethane, trinitrotoluene, icterogen, amanitotoxin, bean poison, diethylstilbestrol, phenylhydrazine, toluylenediamine, arsphenamine, bismuth, mercury, cinchophen, the sulfonamides and liver extract. It is obvious from the foregoing that the substances capable of producing liver damage are extensive in number and variety and may involve many industries and many pharmacologic products. To be sure, the list could be expanded well beyond the limits of the present discussion, but as it stands it is impressive from the point of view of the various hazards that may involve hepatic function in human beings. The above review is extremely comprehensive and is well documented.

In addition to the importance of specific toxins in causing liver damage, it is pertinent to emphasize the continuing role played by various nutritional deficits in the actual production of functional or histologic alterations in the liver. Caloric adequacy in the diet, the inclusion of various substances, such as proteins, specific amino acids and vitamins, particularly those of the vitamin B complex, and the exclusion of excessive amounts of fat are factors that undoubtedly modify the response of the liver to noxious substances. There can be little doubt that deficiency conditions involving one or many factors may be responsible for hepatic damage that would not occur from specific poisons under conditions of completely adequate nutrition. The observations of Miller and Whipple[2] supply ample confirmation of such a statement, as does the work of many others, including Rich, György, Ravdin, and Patek and Post.

Some of the hazards that have been recognized and studied by recent observers should be mentioned. Trinitrotoluene poisoning, for instance, is primarily a civilian wartime problem; during World War I there were 1700 cases in the United States, with 475 deaths.[3] Probably the incidence will be lower during the present war. Toxic necrosis of the liver resulting from trinitrotoluene poisoning is one of its rarer manifestations but is fatal in about one third of the patients so afflicted. The clinical manifestations of this form of poisoning have been thoroughly reviewed by Lane.[4] Although toxic jaundice is relatively infrequent among workers presenting symptoms due to trinitrotoluene intoxication, it is an important manifestation because of the potential severity of the liver damage. Jaundice, when present, usually appears after a short exposure, less than three months, and tends to occur much more frequently in women than in men. In at least half the cases presented by Lane, the liver was palpable and tender. Eight cases are described, with 2 deaths. In the survivors, unusual fatigue was a persisting symptom, and the author speculated on the possible residual of cirrhotic processes, although follow-up studies were not available. In his discussion of this article, Davie mentioned 7 cases, all in women. The autopsy findings revealed acute necrosis of the liver. The exact mode of production of this form of liver poisoning is not known. Attempts to reproduce it experimentally in animals have failed, and it is striking that only a few cases have occurred among large numbers of workers apparently exposed to the same hazard. Palmer, McShane and Lipman[5] report in detail 3 cases of apparent trinitrotoluene poisoning with recovery, the evidence suggesting that the toxic necrosis of the liver was severe in one patient, moderate in the second and slight to moderate in the third. In these cases, jaundice, anilism and gastrointestinal symptoms were characteristically found.

Intoxication by tetrachlorethane has long been recognized. The observations of Gurney[6] are of interest, particularly in relation to the apparent varia-

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tions in susceptibility to this solvent dependent on age. In his series, 277 employees were studied — 158 men and 119 women. Under the conditions of exposure to tetrachlorethane experienced by this group, striking hepatic involvement was noted, and enlargement of the liver was found in nearly 25 per cent of the women but in only 12.6 per cent of the men. Not only was there a great difference in susceptibility based on sex, but it also appeared evident that older persons were much more liable to hepatic damage than younger ones. Of workers under the age of thirty, 9.8 per cent had demonstrable liver enlargement; of those between the ages of thirty-one and fifty, 29.4 per cent showed a similar finding; and in those from fifty-one to seventy years, essentially the same percentage was involved (28.5 per cent). It seems obvious, therefore, that employees exposed to tetrachlorethane should be chosen from young men. Frequent physical examinations are desirable, with particular attention to the size of the liver. Simple laboratory procedures also are indicated at periodic intervals, and determination of the level of the bile pigments in the blood and urine has diagnostic and prognostic value. In some cases in this series, hyperbilirubinemia or the appearance of bile in the urine was the first indication of liver damage. The cephalin flocculation test seemed to give additional valuable evidence.

In view of the widespread use of carbon tetrachloride in industry as well as therapeutically, a case report of acute poisoning following the accidental ingestion of between 30 and 40 cc. of this substance is of interest. Beattie and his collaborators[6] successfully treated such a case, which was unusual because of the large quantity of carbon tetrachloride ingested and because of the successful outcome. The maximum therapeutic dose is 4 cc., and there seemed to be no doubt that the massive dose noted above was ingested and absorbed. Within nineteen hours the liver was easily palpable. Shortly afterward intensive therapy was started, consisting of the intravenous injection of a casein digest-methionine solution, at the rate of 2 cc. a minute. At the end of three hours the infusion was stopped because of chilliness, malaise and muscle aches, and it was noted that the liver was still enlarged and tender, its edge being at the level of the umbilicus. On the following day the liver was no longer tender, and its edge had receded to within 2 cm. of the costal margin. It subsequently became enlarged again, at which time the patient was treated by the oral administration of 2 gm. of methionine in the morning and evening. On the fourth day the patient was asymptomatic, and abdominal palpation revealed a second reduction in the size of the liver to near the costal margin. The subsequent course of events was entirely satisfactory. The use of *dl*-methionine in large doses in this case is of interest, and it is possible that the successful results of treatment were primarily due to the protective effect of this amino acid.

It has long been known that many of the anesthetics commonly employed may result in transient or at times in permanent liver damage. Morrison[7] studied the effects on liver function of seven currently used anesthetics as measured by the concentration of bile salt in the urine. Although the method employed is probably not too acceptable a measure of hepatic function, there can be little doubt that the evidence obtained by this author is reasonably accurate and suggestive. Evipal sodium, cyclopropane and nitrous oxide, under the conditions employed, showed no deleterious effect on liver function as determined by this test. Avertin and chloroform produced evidence of hepatic dysfunction lasting for twenty-four hours. Ether produced a marked disturbance in hepatic function as judged by the concentration of bile salt in surgical-drainage bile, whereas spinal anesthesia resulted in only moderate increases in elimination of bile salt. The conclusions reached in this study are in no sense new, but they are timely because of the many innovations in anesthesia that are employed at present. The chief importance of such findings should be to increase the general awareness of surgeons and anesthetists of the risks that may be run incident to the various types of surgical anesthesia, particularly in patients with potential hepatic damage. Because of the advantages accruing to the use of chloroform in war, it is necessary periodically to stress also its dangers. Avertin should be used with extreme caution in depleted patients and in those with biliary-tract disease, and as has been pointed out on numerous occasions, the use of ether as an anesthetic in jaundiced patients should be associated with great care and with special precautions to prevent anoxia.

The troublesome question of liver damage following the use of arsenicals has been revived because of the large number of patients receiving antisyphilitic treatment in the armed services. The hepatic pathology associated with arsenotherapy has been carefully studied by various observers. In the past, the jaundice has usually been ascribed to injury of the liver parenchyma, and in cases terminating fatally it has been possible to confirm the hepatogenic character of the jaundice by histologic studies that showed marked degenerative changes in the hepatic lobule. Hanger and Gutman[8] in 1940 presented evidence based on liver biopsies that in some cases the icterus was the result of obstructive processes within the bile ducts rather than of injury to the liver parenchyma. In 12 cases of postarsphenamine jaundice there was a preservation of essentially normal hepatic parenchyma, the principal lesion being pericholangitis, with bile thrombi in the finer biliary radicals. In these cases, various laboratory tests indicated little damage to liver-cell function but definite evidence of biliary

obstruction. Although the jaundice persisted for weeks or months, recovery eventually occurred. More recently Dible and McMichael,[9] using the technic of Roholm and Iversen for obtaining biopsy material, studied 35 cases of arsenical jaundice, and in addition, cases of ordinary infectious hepatitis that were regarded as controls. These authors believed that the histologic picture and the sequence of pathologic developments in arsenical jaundice showed no significant differences from those seen in epidemic hepatitis or in the hepatitis seen after serum injections. The histologic appearance of the biopsy specimens did not support the suggestion that either syphilitic lesions of the liver or arsenobenzol poisoning played any part in their production. Although varying degrees of damage were noted, the histologic changes primarily suggested damage of the parenchymal cells.

Riddell and Anderson,[10] using the oral hippuric acid test for liver function, studied a group of 188 patients already under arsenical treatment for early syphilis. Treatment consisted in the employment of neoarsphenamine or Mapharside. These authors attempted to determine whether impairment of the detoxicating function of the liver is directly proportional to the quantity of the arsenical used; whether failure of the detoxicating mechanism precedes the onset of clinical jaundice and the appearance of bile products in the urine by an interval sufficient to allow the clinician to modify the treatment; and whether the hippuric acid test is of prognostic value in postarsenical jaundice. Twenty-seven per cent of the patients receiving arsenical treatment for early syphilis excreted less than the normal amount of hippuric acid in the urine, although they were free from abnormal signs and symptoms, a finding that led the authors to believe that arsenotherapy impairs the normal detoxicating function. On the other hand, they found no direct relation between the results of the hippuric acid test of liver function and the amounts of arsenicals taken. The effect of the arsenicals on the liver, therefore, was thought to be dependent primarily on individual sensitiveness rather than on the quantity given. By means of numerous tests performed during treatment, it was shown that the failure of the detoxicating function detected in this study preceded the onset of jaundice and the appearance of bile products in the urine. Although arsenotherapy was stopped as soon as evidence was obtained of hepatic dysfunction, jaundice resulted in about one third of these cases. Tests performed every two weeks after the development of jaundice showed a steady and sometimes rapid return to normal function. A very low hippuric acid output did not necessarily imply a fatal outcome or irreparable damage to the hepatic detoxifying mechanism, a finding that should occasion little surprise.

In this regard it is of interest to refer to an article by Messinger and Hawkins[11] published in 1940 on modification of arsphenamine liver injury in dogs by dietary measures. Liver injury was trivial when the animals were on a protein diet, and the damage was promptly repaired. A high-carbohydrate intake, although also beneficial, was not so highly protective as the protein diet, and on it the liver injury was sometimes somewhat greater. Progressive jaundice, severe liver injury and fatal intoxication were noted when the animals were kept on high-fat diets during the administration of arsphenamine. An interesting point, which I have confirmed in human beings, was that animals protected by high-protein or high-carbohydrate diets showed a progressive increase in the icteric index when an increase in dietary fat was given, even though no additional arsphenamine was injected. Conversely, dogs on fat-free diets that showed severe intoxication due to arsphenamine injury usually improved immediately when a shift was made to a high-protein and high-carbohydrate diet. These experimental facts are in keeping with many other investigations and are fairly well recognized, but are of special significance in relation to the care of patients who are receiving arsenotherapy for syphilis.

Of the various antisyphilitic arsenicals, Mapharsen seems to be tolerated the best. The studies of Anwyl-Davies[12] provide an interesting comparison between the results obtained after the use of neoarsphenamine and those noted following treatment with Mapharsen. Of 1946 patients treated with neoarsphenamine, the astounding number of 574 (29 per cent) developed jaundice. Of 1147 patients treated with Mapharsen, 146 (12.8 per cent) developed jaundice. Thus the latter drug not only produced less frequent evidence of hepatic damage but was also accompanied by jaundice of much shorter duration than that occasioned by other compounds, and the mortality rate was reduced. Some patients who became jaundiced after the use of neoarsphenamine tolerated Mapharsen without incident.

The possible association of infectious hepatitis (catarrhal jaundice) with arsenical jaundice has always been a moot point. For this reason the report by Mitchell[13] is of interest. From July, 1941, to June, 1942, all soldiers in the Canadian Army in England who exhibited jaundice were hospitalized. Mitchell made a careful study of this group. A considerable number of them were found to be receiving arsenical treatment for syphilis. The clinical severity of the hepatitis encountered was relatively mild. There were no differential features between hepatitis occurring during antisyphilitic treatment and that noted in nonsyphilitic patients not receiving arsenotherapy. As suggested previously, liver biopsies showed a marked similarity of the lesions in the two groups. During the year, 0.16 per cent of the total army personnel were hospitalized for jaundice, exclusive of those suffering from extrahepatic biliary obstruction from various causes. Of these men, 17.8 per cent were syphilitic patients

receiving treatment. The remainder were non-syphilitic patients and presumably suffered from uncomplicated infectious hepatitis. The former group represented 5.84 per cent of all syphilitic patients receiving arsenotherapy during the period. The incidence of clinical jaundice in those patients receiving arsenotherapy for syphilis was over thirty-six times as high as that in the group of syphilitic patients not receiving arsenicals. Jaundice was noted three times as frequently in the patients treated with neoarsphenamine as in those treated with Mapharsen. Deaths from acute yellow atrophy in the treated group numbered 1.47 per cent and in the untreated group 0.95 per cent. During the period reviewed, hepatitis was endemic not only in the Canadian Army in England but also in the civilian population with whom the soldiers mingled. The author suggests that a larger number of cases with infectious hepatitis without jaundice occur than has been hitherto recognized, and that it is the association of two hepatotoxic agents (arsenic and the agent of infectious hepatitis) that produces a higher incidence of infectious hepatitis in patients under arsenotherapy.

In view of recent findings in so-called "post-vaccinal jaundice," the article by Bigger[14] is of interest. This author investigated the possibility that jaundice in syphilitic patients receiving intravenous arsenicals is due to the transmission of a virus from patient to patient. In the clinic under observation it was noted that the same syringe was fitted with a succession of sterile needles and was used for ten or more consecutive treatments. After each injection the syringe was thoroughly washed with sterile water and a 1:1000 solution of biniodide, five washings in all. It had been presumed that the procedure used would remove the few drops of blood drawn into the syringe at the beginning of each injection, but experiments showed that the method of cleaning the syringes was not sufficient to remove all the living organisms from it when these were present in the blood. A virus might thus pass from patient to patient in clinics where the same or similar technics were used. Such a finding is extremely suggestive as helping to explain, at least in part, the incidence of jaundice in this particular group of patients. The suggestion of the author that a thoroughly boiled syringe be used for each patient is obviously sound.

Rössling[15] studied the effect of arsenic on the liver in relation to acute and chronic forms of damage. From a variety of observations, he concluded that cirrhosis of the Laennec type due to arsenical poisoning alone is unlikely, and stresses the importance of considering the additive effects of such substances as alcohol, lead, nicotine and copper and those of infections, metabolic disturbances and cachexia. Certainly the combination of hepatic infection and malnutrition may well form the background for specific toxic damage to the liver when the dosage of the poison is minimal. The summation effect of several factors in producing liver damage is also mentioned by Kulchar and Reynolds[16] in a discussion of bismuth hepatitis. Although it can hardly be stated that liver damage from bismuth is a generally accepted fact, the survey of 120 cases made by these authors is of considerable interest. Jaundice developed in this group of patients during courses of bismuth therapy for syphilis. Except for 2 patients, all were in the latent stage of the disease. Half the entire group had received varying amounts of treatment prior to entry, but none of these patients gave a history of previous jaundice. In over 8 per cent of the patients treated, there was a recurrence of hepatitis with a resumption of bismuth therapy. The effect of previous arsenical therapy, as well as the less evident factors of diet, alcohol and intercurrent infection, was thought to have predisposed the liver to damage from bismuth.

Reports on hepatic damage following sulfonamide therapy have been occasionally presented. In most, if not all, cases such damage has appeared to be the result of an individual hypersensitivity or an organ hypersensitivity rather than of overdosage. The observations of Machella and Higgins[17] are striking and worthy of comment. These authors carried out four separate experiments devised to determine the effect of sulfanilamide on the already damaged liver or on the liver predisposed to damage by a recognized procedure. The drug was administered to rats in which hepatitis had been induced by carbon tetrachloride, to a second group in which hepatitis was being induced by the same means, to a third group receiving alcohol and finally to a group in which obstructive jaundice had been induced by ligation of the common duct. In the animals in which hepatitis had already been produced by carbon tetrachloride, sulfanilamide did not increase the damage to the liver but appeared to lessen it; in the second group, the drug did not impede regeneration of the liver after the administration of carbon tetrachloride had been discontinued. In the animals receiving alcohol and sulfanilamide, no damage resulted to the hepatic cells, although in some of the animals receiving only alcohol fat was deposited in the liver. In the animals with extrahepatic biliary obstruction, no detectable injury to the liver not ascribable to the biliary obstruction was produced. On the basis of these experiments, reported in 1942, Forbes and Evans[18] carried out further experiments on the protective action of sulfanilamide against hepatic damage from chloroform. These studies were made primarily because of the desirability in modern warfare of such an anesthetic, which is not inflammable and can be transported in small bulk. Acute poisoning was produced, and the animals were sacrificed twenty-four hours later. Histologic examination of the livers showed that the oral administration of

sulfanilamide apparently exerted a protective action against damage to the liver from the inhalation of chloroform in both rats and rabbits. On the basis of these experiments, the authors suggest that sulfanilamide or some other sulfonamide compound be given preoperatively to wounded men who are to be anesthetized with chloroform, and stress the wisdom of giving the drug soon enough to obtain a therapeutic level in the blood stream and liver before the administration of the anesthetic.

That sulfathiazole and sulfadiazine do not necessarily constitute a threat to hepatic efficiency in the treatment of bacterial infections is suggested by the studies of Peterson, Deutsch and Finland.[19] These authors report a series of 37 patients who showed evidence of acute or chronic liver damage and who, for various reasons, received one or the other of these drugs in full therapeutic doses. Studies were made to determine the effect of the drug on hepatic function. In patients with acute hepatitis and bacterial infection, sulfonamide therapy was almost always accompanied by improvement in hepatic function parelleling improvement in the underlying infection. In patients with chronic liver damage, there was no aggravation of the hepatic condition during the administration of the drug. There was some apparent improvement in the cases in which bacterial infection was added to hepatic injury. On the other hand, severe toxic effects, other than those of direct injury to the liver, were unusually frequent in patients with portal cirrhosis and intercurrent infection. These undesirable reactions were about twice as frequent after the use of sulfathiazole as after treatment with sulfadiazine. The authors conclude that the presence of liver damage should not be construed as a contraindication to therapy with sulfathiazole or sulfadiazine in patients with bacterial infections against which these drugs are effective, sulfadiazine being the drug of choice. Caution should be exercised in the administration of sulfonamide compounds in patients with severe portal cirrhosis of the liver.

That sulfonamide therapy may occasionally result in direct damage to the liver, however, is indicated from various recent clinical reports. Menten and Andersch[20] report, out of approximately 300 autopsies performed during three consecutive years, 38 cases of liver disease in children who had had sulfonamide therapy. Pathologic changes included toxic necrosis of the liver in 3 patients, toxic central necrosis in 9 patients and serous hepatitis and beginning toxic central necrosis in the remainder. No relation could be established between the sulfonamide dosage and the development of liver lesions. The Gray colloidal-gold test of liver function was positive in 13 per cent of the children studied, and slightly positive in an additional 20 per cent. No correlation was found between the amount and duration of therapy and the colloidal-gold reaction. Like all recent observers, these authors believe that inadequate nutrition may render the liver more vulnerable to the sulfonamides. They stress particularly protein depletion and an inadequate intake of vitamin B. Cantarow and Wirts[21] mention the presence of hyperbilirubinemia following the administration of sulfonamides in an important number of cases. Twenty patients were studied, and increases of blood bilirubin were noted at periods ranging from one to seven days after the institution of sulfonamide therapy. A return to normal followed in every case after cessation of treatment. Other evidence of hepatic functional impairment was demonstrated in 2 cases treated with sulfanilamide, in 3 cases following the use of sulfathiazole, in 2 after sulfapyridine and in 3 after sulfadiazine. Hyperbilirubinemia occurred after the administration of varying amounts of the drugs and with widely varying sulfonamide concentrations in the blood. When one considers the total number of patients receiving sulfonamide therapy in one form or another without deleterious effects on hepatic function, and the paucity of cases such as those already cited, one is forced to conclude that in most cases these drugs do not cause tremendous danger to the liver, particularly when a proper indication for their employment exists. Thus, Anglem and Clute[22] cite 75 cases in which intraperitoneal sulfanilamide was used following gastrointestinal resections, with a toxic reaction to the drug in only 1 case. In this case a toxic hepatitis occurred, but recovery took place.

The potential damage to the liver from the use of tannic acid in the treatment of burns has been recorded by several observers. With newer methods of treating burns, this hazard will presumably become of little or no importance. The possibility of such danger, however, should be mentioned if for no other reason than to stress the inferiority of tanning to other procedures that are less dangerous as well as more efficacious for the treatment of such common injuries. That hepatic damage may result from serious burns of large areas of the body without the addition of any chemotherapeutic factor is the assumption of Boyce.[23] This author discusses the hepatic factor in burn cases from experimental, clinical, laboratory and autopsy aspects. The article is of particular interest in relation to the unexpected fatalities that occasionally occur in slightly burned persons. It is quite possible that in these cases certain toxic factors associated with the burn exist that have produced a minimal amount of liver damage, and that additional therapeutic measures may provide the necessary factor for ultimate fatal poisoning of the liver. An autopsy report by Duffin[24] shows what seem to be the characteristic findings associated with tannic acid poisoning of the liver. In this case, about one twelfth of the body surface was burned, and the treatment was essentially that of tanning. Icterus developed

on the second day and progressed rapidly, with concomitant enlargement of the liver. On the eighth day, however, the jaundice had diminished and the liver was no longer palpable, but because of intercurrent pneumonia death occurred on the tenth day. An autopsy showed intense central and midzonal necrosis. A careful experimental study of the relation of tannic acid to liver necrosis occurring in burned patients was published in 1942 by Wells, Humphrey and Coll.[25] Central necrosis of the hepatic cells was noted not only in 4 patients who died following such treatment for burns but also in a large number of animals experimentally injected with tannic acid. The degree of hepatic damage in general varied directly with the amount of tannic acid injected. Further observations were made by Forbes and Evans,[26] who also showed that in rats tannic acid injections were hepatotoxic. These authors, moreover, found that no protection was afforded either by the oral or subcutaneous administration of sulfanilamide or by the subcutaneous administration of xanthine.

That massive burns predispose to liver damage, even in the absence of coagulating agents used in burn therapy, is indicated by the studies of Hartman and Romence.[27] Large experimental burns resulted in engorgement of the sinusoids of the liver, especially in the central areas. The introduction of coagulating agents — tannic acid, ferric chloride and silver nitrate — increased the incidence of degeneration and necrosis of the liver cells. Tannic acid used as a wet dressing produced clinical jaundice and central necrosis; the administration of subcutaneous tanning produced liver necrosis in 25 per cent of the animals; and when given intraperitoneally, it caused necrosis in 33 per cent. Various tannic acid preparations were employed, and similar results were obtained with each. Silver nitrate administered subcutaneously produced necrosis and edema at the site of injection and, at the same time, degeneration, hemorrhage and necrosis of the liver, but not the clinical jaundice that was observed following the use of the tannates. Ferric chloride introduced subcutaneously also produced necrosis, edema and hemorrhage at the site of inoculation, and hepatic lesions, with clinical jaundice, that resulted in death. Clark and Rossiter[28] obtained further information regarding the toxicity of tannic acid by following liver function in rabbits after the use of this drug. Impairment of liver function in these animals was demonstrated by intravenous galactose-tolerance tests. Barnes and Rossiter[29] also carried out experiments on guinea pigs and mice with tannic acid and sodium tannate that were entirely in keeping with the foregoing. After application of tannic acid to the raw area produced in guinea pigs by burns to the extent of one third of the body surface, there was slight liver damage, which was definitely greater than that seen in untreated animals similarly burned.

The harmful effect of other therapeutic agents on hepatic function has also attracted attention. Krupski et al.[30] studied the effect of caffeine on the liver in rabbits. Solutions containing several milligrams per hundred cubic centimeters did not affect the oxygen consumption of perfused rabbit livers, although higher concentrations (100 mg. per 100 cc.) increased the oxygen uptake. When the initial caffeine concentration was as high as 200 mg. per 100 cc. in the perfused blood, the final caffeine concentration after one hour or more was 17.5 per cent of the initial caffeine concentration. It is evident that the liver progressively lost the ability to destroy caffeine when the drug was administered in concentrations above 200 mg. per 100 cc.

It has been generally recognized that liver damage is accompanied by an impaired tolerance to morphine and other alkaloids. Gross[31] carried out a study on the effect of liver damage on morphine conjugation in tolerant and nontolerant dogs maintained on a constant diet and constant water intake. Urinary morphine determinations were made before and after liver damage with the animals on a constant dose of morphine. Control observations on the damage produced by carbon tetrachloride were obtained by repeated determinations of bromsulfalein excretion. The urine was analyzed for total, free and easily hydrolyzable morphine. The fraction of morphine that was hydrolyzable with difficulty was determined by the difference between the last two figures and the total urinary morphine. The author's earlier observation that liver damage by chloroform produced an increase in free morphine excretion also held true when carbon tetrachloride was used as the damaging agent. In addition to the marked increase in free morphine after carbon tetrachloride injury, there was a decrease in the excretion of the easily hydrolyzable fraction of combined morphine. Since the total recoverable morphine was not materially altered and the portion hydrolyzed with difficulty remained fairly constant, the easily hydrolyzable compound appeared as free morphine. One may conclude from these experiments that the easily hydrolyzable form of conjugation is the only one that takes place in the liver. Liver damage apparently inhibits the conjugation of morphine to a certain extent, as shown by the fact that the free morphine found in the urine increased without any corresponding increase in the total morphine excreted. These studies confirm and partially explain the known clinical fact that ordinary clinical doses of morphine may present special hazards when administered to patients with liver disease.

Although the exact effect of alcohol on the liver is imperfectly understood, there can be little reasonable doubt that this substance is a noxious agent in the presence of hepatic damage. It is generally accepted that the primary oxidation of alcohol occurs in the liver. Partial removal of or extensive damage to the liver in experimental animals is fol-

lowed by a decrease in the rate at which alcohol is oxidized. Lolli and Rubin[32] studied in rats the rate of disappearance of alcohol from the blood in experimentally produced obstructive jaundice. Obstruction to the flow of bile was induced by ligation of the common bile duct, and alcohol was administered intraperitoneally. A marked decrease in the rate of disappearance of alcohol from the blood occurred in the rats with obstructive jaundice. This impairment of liver function as related to alcohol metabolism appeared as early as twenty-four hours after jaundice had set in.

The toxic effect of cinchophen on the liver is now generally accepted as one of the potential dangers in the use of this drug as a therapeutic agent in gout or other conditions. The studies of Annegers and his colleagues[33] on the effect of cinchophen on secretion of cholic acid emphasize the undesirable results that may occur after its use, and in particular stress the variations in susceptibility to the drug in the same animal and in different animals. Using large doses of cinchophen, these authors sometimes noted a marked temporary depression of the synthesis and secretion of cholic acid. Complete temporary suppression of cholic acid secretion sometimes occurred in the absence of anorexia and objective gastrointestinal symptoms. Most of the animals recovered from the damage to this particular hepatic function during repeated administrations of cinchophen. Since an extremely sensitive animal in the series recovered from the impairment of cholic acid synthesis and secretion but nevertheless died within a week, the authors concluded that death after the administration of cinchophen is due to some vital function of the liver unrelated to this particular function. Such a finding emphasizes two points of importance: the potential danger associated with the use of cinchophen, and the importance of the use of more than one test for hepatic function in determining serious liver damage.

A clinical consideration of extreme importance at the present time is the possible effect of malaria and antimalaria drugs on the liver. Alterations in liver function during the course of therapeutic malaria have been investigated by Kopp and Solomon.[34] Nine patients were studied while under hospital treatment for general paresis, no other condition having been demonstrated prior to treatment. Three of the patients had received trivalent and pentavalent arsenicals before malaria therapy. The patients were allowed four to twelve paroxysms, after which the malaria was treated by the administration of quinine. Moderate bromsulfalein retention, a marked reduction in cholesterol esters, a moderate fall in phospholipids, diminished hippuric acid excretion and a strongly positive cephalin flocculation test were noted. Evidences of impairment of liver function were transient, lasting usually three to six weeks after the termination of malaria. The cephalin flocculation test was the last index to revert to normal. It is highly probable that clinical malaria as observed at the present time among the armed forces is not primarily a source of serious damage to the liver. Simpson and his collaborators,[35] for example, state that jaundice occurred in only 1 per cent of the cases observed at a general base hospital in the South Pacific. This report covers a total of 4647 admissions, and the observations were carried out in one of the most heavily malarialized areas in the world. Only 1 death occurred in this entire group of patients, and this case was complicated by postvaccinal hepatitis, a further example of the probable danger accruing to a summation of toxic insults to the liver. Quinine or atabrine, or both, were employed in the treatment of these cases.

That underlying liver damage may modify the metabolic destruction of quinine might be expected, and the experimental results of Anderson, Cornatzer and Andrews[36] confirm such a hypothesis. These investigators found that removal of half to one third of the liver in rats caused an increase in urinary excretion of quinine of 72 to 143 per cent over that observed in the same animals when intact. When a period of four weeks was allowed for hepatic regeneration, excretion again fell to normal levels. Damage to the livers of dogs following chloroform anesthesia resulted in the maintenance of higher levels of quinine in the blood stream for a longer period of time than normal and also raised the percentage of urinary excretion. Lengthening the period of chloroform anesthesia increased this effect. After an interval of four months in which normal conditions were re-established, the blood levels and urinary excretion following standard quinine dosage in the same animal were found to remain normal. These results not only indicate the presence of some agent in the liver that is evidently active in the metabolic destruction of quinine but also suggest that underlying liver disease may seriously alter the therapeutic effects of this drug.

The effect of atabrine on the liver is still not clear. Annegers and his group[37] studied the retention of atabrine in animals with particular relation to its excretion in the bile and urine and its effect on the cholic acid output. In human beings, atabrine dehydrochloride causes occasional toxic reactions with predominant gastrointestinal symptoms. In some, damage to the liver seems to occur, and this is believed to be due to a specific idiosyncrasy, as is probably the case with cinchophen, or to malnutrition. In experiments on white rats and dogs, the drug was rapidly destroyed or chemically modified in the body. It was not stored to any significant extent in the liver, spleen or muscles, and largely disappeared from the body within ten days. On the basis of its effect on the cholic acid output, it was believed that the drug had hepatotoxic action in some cases, but it did not appear to result in a conjugated form that was particularly harmful.

Serious and sometimes fatal liver derangement is occasionally noted during pregnancy, although the exact mechanism causing it is far from clear. Conversely, the course of pregnancy may be seriously complicated by hepatic damage. Fels and de Eandi[38] studied in animals the effect of partial hepatectomy on the course of pregnancy. They concluded that extirpation of one third of the liver does not prevent the normal course of pregnancy, although excision of half or more was followed by immediate termination of pregnancy. In the animals studied, pregnancy again occurred and proceeded normally nine days after removal of half the liver, an indication of the remarkable regenerative power of this organ.

A study of the hepatic changes produced by estrone, estradiol and diethylstilbestrol was made by MacBryde, Castrodale, Helwig and Bierbaum.[39] These preparations of natural and synthetic estrogens were administered in estrogenically equivalent doses. To avoid possible complicating factors in the interpretation of hepatic changes, the animals were killed before hemorrhage occurred. The results of the experiments showed that large doses of the natural estrogens, such as estrone, and of estradiol benzoate produced changes in the liver, bone marrow and peripheral blood of dogs that were indistinguishable from those produced by the synthetic estrogen diethylstilbestrol. These changes consisted of fatty degeneration and hydropic degeneration of cells. In general, alterations in the parenchymal cells were not widespread or prominent. The danger of hepatic damage following the therapeutic use of these substances seems to be relatively negligible, except possibly in conditions of malnutrition or in the presence of existing liver damage.

It is rare that the performance of various tests for hepatic function is accompanied by danger to the organ. For this reason, the report by Kinsey and Wright[40] on severe reactions following the ingestion of sodium benzoate in a patient with extensive liver damage is of interest. This patient was suffering from marked hepatic insufficiency. Attempts to measure the degree of liver impairment by the use of the hippuric acid test resulted on two occasions in identical reactions, coming on about four hours after the ingestion of sodium benzoate and consisting of severe substernal pain, shock, increased icterus and granulocytopenia. The reaction following the performance of the second test was the severer and suggested that the liver was sufficiently damaged to be unable to conjugate the sodium benzoate to a relatively nontoxic substance.

A discussion of the various liver-function tests in current use is not indicated in this article. Reference will be made to one recent study, however, because of its application to ordinary bedside observations that may be made in connection with the course and prognosis of liver disease. In 1935, Eaton and I[41] described in detail the changes in water elimination noted in various phases of hepatic disease. The occurrence of spontaneous diuresis has always appeared to be one of the signs pointing to an improving prognosis and to successful therapy. Adlersberg and Fox[42] have carried out interesting experiments on the diagnostic significance of changes in water metabolism as correlated with the nature and extent of hepatic damage. In the early stages of experimental intoxication with mild hepatic damage, water intake caused an early and extensive diuresis, but in the later stages with considerable organic damage, diuresis was delayed and diminished with water retention in the tissues. In addition to animal experiments, 23 patients with parenchymatous liver disease were studied. These clinical observations confirmed the experimental evidence and emphasized the importance of simple bedside studies that may clearly reveal the course of hepatic efficiency as influenced by various types of liver intoxication.

References

1. Ottenberg, R., and Spiegel, R. Present status of non-obstructive jaundice due to infectious and chemical agents: causative agents, pathogenesis, inter-relationships, clinical characteristics. *Medicine* **22**:27-71, 1943.
2. Miller, L. L., and Whipple, G. H. Chloroform liver injury increases as protein stores decrease: studies in nitrogen metabolism in these dogs. *Am. J. M. Sc.* **199**:204-216, 1940.
3. Palmer, W. L., McShane, G. S., and Lipman, W. H. Toxic necrosis of liver from trinitrotoluene: report of three cases. *J. A. M. A.* **123**:1025-1027, 1943.
4. Lane, R. E. Discussion on trinitrotoluene poisoning. *Proc. Roy. Soc. Med.* **35**:556-558, 1942.
5. Gurney, R. Tetrachlorethane intoxication: early recognition of liver damage, and means of prevention. *Gastroenterology* **1**:1112-1126, 1943.
6. Beattie, J., Herbert, P. H., Wechtel, C., and Steele, C. W. Studies on hepatic dysfunction. I. Carbon tetrachloride poisoning treated with casein digest and methionine. *Brit. M. J.* **1**:209-211, 1944.
7. Morrison, L. M. Study of hepatic toxicity with seven currently used anesthetics. *Rev. Gastroenterol.* **10**:171-182, 1943.
8. Hanger, F. M., Jr., and Gutman, A. B. Postarsphenamine jaundice apparently due to obstruction of intrahepatic biliary tract. *J. A. M. A.* **115**:263-271, 1940.
9. Dible, J. H., and McMichael, J. Pathology of arseno-therapy jaundice. *Brit. J. Ven. Dis.* **19**:102-108, 1943.
10. Riddell, R. W., and Anderson, T. E. Hippuric acid liver-function test during treatment with arsenicals. *Lancet* **1**:275, 1944.
11. Messinger, W. J., and Hawkins, W. B. Arsphenamine liver injury modified by diet. Protein and carbohydrate protective, but fat injurious. *Am. J. M. Sc.* **199**:216-225, 1940.
12. Anwyl-Davies, T. Post-arsenical jaundice and dermatitis: survey of records from St. Thomas's Hospital, 1929-1941. *J. Roy. Nav. M. Serv.* **29**:154-169, 1943.
13. Mitchell, H. S. Incidence of catarrhal jaundice compared with jaundice following arsenotherapy for syphilis. *Canad. M. A. J.* **48**: 94-96, 1943.
14. Bigger, J. W. Jaundice in syphilitics under treatment: possible transmission of virus. *Lancet* **1**:457, 1943.
15. Rössling, P. Disturbances of liver with special reference to cirrhosis of liver from arsenical poisoning. *Arch. f. Gewerbepath u. Gewerbehyg.* **11**:131, 1941.
16. Kulchar, G. V., and Reynolds, W. J. Bismuth hepatitis: survey of 121 cases. *J. A. M. A.* **120**:343-346, 1942.
17. Machella, T. E., and Higgins, G. M. Effect of sulfanilamide on experimentally damaged liver. *Am. J. M. Sc.* **204**:194-201, 1942.
18. Forbes, J. C., and Evans, E. I. Protective action of sulfanilamide against hepatic damage from chloroform inhalation. *War Med.* **4**: 418-421, 1943.
19. Peterson, O. L., Deutsch, E., and Finland, M. Therapy with sulfonamide compounds for patients with damage to liver. *Arch. Int. Med.* **72**:594-612, 1943.
20. Menten, M. L., and Andersch, M. A. Hepatic damage associated with sulfonamide therapy in infants and children. I. Morphologic pathology. II. Changes in liver function test during sulfonamide therapy. *Ann. Int. Med.* **19**:609-628, 1943.
21. Cantarow, A., and Wirts, C. W. Hyperbilirubinemia following administration of sulfonamides. *J. Lab. & Clin. Med.* **28**:71-74, 1942.
22. Anglem, T. J., and Clute, H. M. Intraperitoneal use of sulfanilamide in gastrointestinal resections. *New Eng. J. Med.* **229**:432-434, 1943.
23. Boyce, F. F. Hepatic (hepatorenal) factor in burns. *Arch. Surg.* **44**: 799-818, 1942.
24. Duffin, J. D. Liver necrosis following burns. *Canad. M. A. J.* **47**:138, 1942.
25. Wells, D. B., Humphrey, H. D., and Coll, J. J. Relation of tannic acid to liver necrosis occurring in burns. *New Eng. J. Med.* **226**: 629-636, 1942.

26. Forbes, J. C., and Evans, E. I. Tannic acid and liver necrosis. *Surg. Gynec. & Obst.* **76**:612, 1943.
27. Hartman, F. W., and Romence, H. L. Liver necrosis in burns. *Ann. Surg.* **118**:402-416, 1943.
28. Clark, E. J., and Rossiter, R. J. Liver function in rabbits after injection of tannic acid. *Lancet* **2**:222, 1943.
29. Barnes, J. M., and Rossiter, R. J. Toxicity of tannic acid. *Lancet* **2**: 218-222, 1943.
30. Krupski, A., Kunz, A. F., and Almasy, F. Das Verhalten der überlebenden Kaninchenleber gegenüber Kaffein. *Schweiz. med. Wchnschr.* **22**:585-587, 1941.
31. Gross, E. G. Effect of liver damage on urinary morphine excretion. *Proc. Soc. Exper. Biol. & Med.* **51**:61-63, 1942.
32. Lolli, G., and Rubin, M. Rate of disappearance of alcohol from blood in obstructive jaundice. *Quart. J. Stud. Alcohol* **4**:183-186, 1943.
33. Annegers, J. H., Snapp, F. F., Ivy, A. C., and Atkinson, A. J. Effect of cinchophen on secretion of cholic acid. *Arch. Int. Med.* **73**:1-6, 1944.
34. Kopp, I., and Solomon, H. C. Liver function in therapeutic malaria. *Am. J. M. Sc.* **205**:90-97, 1943.
35. Simpson, W. M., et al. I. Experiences with malaria at advance base in South Pacific: report of 4647 admissions at. . . . *U. S. Nav. M. Bull.* **41**:1588-1595, 1943.
36. Anderson, C. E., Cornatzer, W. E., and Andrews, J. C. Role of liver in metabolic destruction of quinine. *J. Pharmacol. & Exper. Therap.* **79**:62-69, 1943.
37. Annegers, J. H., et al. Retention of atabrine in animal body: excretion in bile and urine and effect on cholic acid output. *War Med.* **4**:176-186, 1943.
38. Fels, E., and de Eandi, F. Partial hepatectomy and pregnancy. *J. A. M. A.* **123**:785, 1943.
39. MacBryde, C. M., Castrodale, D., Helwig, E. B., and Bierbaum, O. Hepatic changes produced by estrone, estradiol and diethylstilbestrol. *J. A. M. A.* **118**:1278-1281, 1942.
40. Kinsey, R. E., and Wright, D. O. Reaction following ingestion of sodium benzoate in patient with severe liver damage. *J. Lab. & Clin. Med.* **29**:188-196, 1944.
41. Jones, C. M., and Eaton, F. B. Prognostic significance of spontaneous diuresis in acute or subacute disease of liver. *New Eng. J. Med.* **213**:907-918, 1935.
42. Adlersberg, D., and Fox, C. L., Jr. Changes of water tolerance test in hepatic disease. *Ann. Int. Med.* **19**:642-650, 1943.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**
BENJAMIN CASTLEMAN, M.D., *Acting Editor*
EDITH E. PARRIS, *Assistant Editor*

CASE 30251

PRESENTATION OF CASE

A fifty-six-year-old toolroom clerk was admitted to the hospital complaining of increasing weakness.

The patient had been well until a year prior to admission, at which time he noted generalized weakness becoming progressively more pronounced. This was accompanied by gradual weight loss, amounting to 25 pounds. Six months before entry he had severe diarrhea, lasting about two weeks and associated on one occasion with nausea and vomiting. This was followed by a rise in temperature (105.2°F.) and a diffuse cherry-red erythema over the upper portion of the body. This episode lasted for about three days, the temperature gradually reaching normal. Following it, weakness was more pronounced, and weight loss more rapid.

Because of these symptoms he attended a local outpatient department, where he was found to have anemia (2,500,000 red cells, with 7 per cent reticulocytes). The spleen, but not the liver, was palpable. The urine showed a ++++ test for albumin, with rare hyaline casts. The stomach content contained no free hydrochloric acid, and was positive for occult blood and lactic acid. Treatment with Feosol, yeast and dilute hydrochloric acid resulted in little improvement and three months later he was finally admitted to a local hospital, where he remained for five weeks. At that time the liver was palpable five fingerbreadths below the costal margin; the spleen was still palpable. The red-cell count was 2,750,000, with 10.5 gm. of hemoglobin; the mean corpuscular volume was 109 cubic microns, the mean corpuscular hemoglobin 38 millimicrograms, and the reticulocyte count 0.4 to 2 per cent. The bleeding, clotting and prothrombin times were normal. The icteric index was within normal range. The serum protein was 8.7 gm. per 100 cc., with an albumin-globulin ratio of 2. The serum phosphatase was 13 Bodansky units per 100 cc. X-ray studies of the chest, gastrointestinal tract, long bones and pelvis were negative. A sternal marrow biopsy revealed no characteristic cellular picture, but suggested pernicious anemia. A liver biopsy revealed almost complete replacement of normal tissue cells by dense fibrous tissue in which there was bile-duct proliferation. The liver on peritoneoscopy appeared grossly enlarged and roughly granular.

Following discharge, the patient was treated with yeast and liver by mouth and parenterally, with no response, and he was finally admitted to this hospital two months later.

Physical examination revealed a pale man, showing evidence of recent weight loss. A spider angioma was present on the neck. An area of diminished resonance and inconstant inspiratory rales was present at the right base. The heart revealed a soft systolic murmur, not transmitted, over the pulmonic area. The liver edge extended from the right iliac crest to the costal margin in the left midclavicular line and felt somewhat nodular. The lower pole of the spleen was palpable. The prostate was slightly enlarged. There was questionable pitting edema of the ankles.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 99.2°F., the pulse 80, and the respirations 20.

Examination of the blood revealed a red-cell count of 2,570,000, with 8.5 gm. of hemoglobin. The white-cell count was 5700, with 49 per cent neutrophils, 30 per cent lymphocytes, 20 per cent monocytes and 1 per cent eosinophils. There were a few macrocytic red cells. The urine revealed a ++++

*On leave of absence.

test for albumin, and occasional red cells, white cells and granular casts. A bromsulfalein test showed 30 per cent dye retention. The van den Bergh was within normal limits. The protein ranged from 6.2 to 7.0 gm. per 100 cc., with an albumin-globulin ratio of 2.1 to 2.5. The blood cholesterol was 122 mg. per 100 cc., the calcium 10.7 mg., and the phosphorus 4.8 mg. The alkaline phosphatase was 4.8 units, and the acid phosphatase 1.8 units per 100 cc. A Congo red test was negative for amyloid. The prothrombin time was 22 seconds (normal, 16 seconds). A blood Hinton test was negative.

A roentgenographic examination of the chest, a gastrointestinal series and a barium enema revealed no abnormalities, except an enlarged liver and spleen.

On the sixteenth hospital day a peritoneoscopy revealed an enlarged liver, exactly as palpated, with a tongue of liver tissue extending down below the umbilicus in the right lower quadrant and flank. The surface was mottled, reddish-yellow and questionably granular; there was a fairly sharp edge. There was no evidence of neoplastic implants. The spleen was about twice its normal size, smooth and dark brown. There was no ascites. The liver was biopsied.

Differential Diagnosis

Dr. Chester S. Keefer*: The patient was fifty-six years of age and had been ill for over a year with constitutional symptoms and loss of weight, increasing fatigability and weakness. In the past there had been one episode of diarrhea of two weeks' duration, during which time he developed a temperature of 105°F., and a diffuse cherry-red erythema over the upper part of the body. I am unable to explain that episode. It has occurred to me that perhaps this man had received some sulfonamide from one of his physicians for the treatment of diarrhea and developed the fever and skin eruption as a result. It is not stated, however, in this record whether that was known. There are few patients who have diarrhea of more than two or three days' duration who do not receive one of the sulfonamides; some of them develop fever and a skin eruption if the drug is continued for a period of seven days or longer.

One might, for the sake of mental exercise, indulge in some speculations concerning what other disorders cause diarrhea and skin eruptions. We know that certain strains of hemolytic *Staphylococcus aureus* are capable of liberating exotoxin as well as endotoxin, and occasionally these patients show a typical scarlatiniform eruption associated with infection. These infections are of short duration, the skin lesions are exfoliative in character, and the gastrointestinal symptoms appear within a short period after the ingestion of food. The common foods that are contaminated by the staphylococcus, of course, are custard pies and the filling of cream puffs. If the organisms grow freely, they liberate an exotoxin and some strains liberate an erythrogenic toxin, which is exceptionally difficult to distinguish from the streptococcal erythrogenic toxin. Antiscarlatinal antiserum will, on occasion, blanch the rash of staphylococcal infection.

When this patient was admitted to the first outpatient department he had an anemia with enlargement of the spleen and albuminuria. This anemia apparently did not respond to any form of treatment that was prescribed — iron, yeast and dilute hydrochloric acid. One might expect that the anemia would be refractory to hydrochloric acid, but not to the iron or the yeast. On admission to that hospital the anemia was still present and was hyperchromic. The sternal marrow biopsy showed nothing definite but was suggestive of pernicious anemia. The liver biopsy showed dense fibrous tissue, with bile-duct proliferation. That is the picture that one might see in extensive cirrhosis of the liver. With fibrosis, the bile ducts make a frantic effort to proliferate and to join up with the new nodules in an attempt to excrete bile from these cells. I think that we cannot accept that conclusively, however, in light of the fact that the liver increased in size rather than decreased. In any event it seems clear that this anemia was refractory and did not respond to liver, and that it was not an ordinary pernicious anemia.

The physical examination on the last admission says that a spider angioma was noted over the neck. When one finds spider angiomas it is usually suggestive that the patient has liver disease. These spider angiomas attracted attention in the medical literature over twenty-five years ago. If you read about the old descriptions of cirrhosis of the liver they are freely discussed. Then, for a long time no one paid any attention to them, but in the last few years a great deal of interest has again been shown. They are dilated arterioles, and when examined carefully, they tend to occur only on the upper half of the body and, for some curious reason, over the area drained by the superior vena cava. It has been suggested that the disturbances in the estrogenic hormones that take place in liver disease may be responsible for these angiomas. In any event it was noted here that there was a spider angioma on the neck, suggesting that the man had liver disease.

Then, once again, there were enlargement of the liver and spleen, anemia that did not respond and albuminuria. Someone expressed the opinion that this man may have had amyloid disease because of the albuminuria, the big liver and the enlarged spleen. This was a good suggestion, but the Congo red test was negative. A bromsulfalein test showed

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that he retained at least 30 per cent of the dye, indicating that he had a disturbance of hepatic function.

The x-ray studies were negative except that they showed an enlarged liver. Finally, there was another peritoneoscopy, and they found that the liver was still large; a biopsy was taken, and Dr. Castleman will shortly tell you the diagnosis.

The question that arises in this patient, of course, is, Was this simply a case of cirrhosis of the liver, or was there some process superimposed on the cirrhosis? If one assumes that it was just cirrhosis, it is difficult to explain why the liver was enlarged. One must believe the record, which states that the liver increased in size from the first admission until the time of the biopsy that disclosed the answer. Patients who have an enlarging liver usually have some infiltrating process in that organ. The one type of liver disease that is associated with fibrosis, and even with cirrhosis, and a very large liver is the fatty liver. They may reach enormous proportions, weighing 4000 to 5500 gm. The story in these cases is usually characteristic. The patient is either a heavy gin or whisky drinker, consuming anywhere from a pint to a quart a day over many years. There is no evidence that this was an enlarged fatty liver.

The first examination, with the tender spleen and hyperchromic anemia, certainly suggests that he might have had pernicious anemia, but that was not borne out by the therapeutic test and did not seem to be borne out by the gradual enlargement of the liver. One may encounter a refractory form of macrocytic anemia in patients with cirrhosis of the liver or some disorder of the bone marrow, such as a lymphoma. That naturally raises the question whether this patient might have had a lymphoma with a big liver, a big spleen and an anemia that was macrocytic in type. From the original biopsy, however, there is no evidence that there was lymphocytic infiltration of the liver. The bone marrow showed no changes consistent with the diagnosis of lymphoma. So we have no basis in this record for making such a diagnosis.

It seems to me that the likeliest explanation for this case is that the patient had a cirrhosis of the liver on which was superimposed a carcinoma, but when one makes that diagnosis one is always treading on dangerous ground. There are two forms of primary liver-cell cancer. One is a hepatoma, in which there is an initial lesion that expands and usually metastasizes by way of the veins, so that there is one large lesion with multiple small or varying sized nodules in the liver, with few metastases elsewhere. The other type of liver-cell carcinoma usually arises from the small bile ducts. There is some evidence in this case that diffuse fibrosis of the liver was present, with bile-duct proliferation. That is somewhat suggestive that this proliferation of the bile ducts was not just the type that one sees associated with cirrhosis of the liver with disorganization of the tissue. The one point that I cannot explain on the basis of uncomplicated cirrhosis of the liver is the fact that the liver was so large. We know that it was fibrous and that the liver increased in size. These are the points that lead me to suspect that this man had cirrhosis of the liver with a superimposed carcinoma of the bile-duct-cell type. That is the best diagnosis that I can offer; perhaps, in addition, the patient had some degree of nephrosclerosis.

DR. BENJAMIN CASTLEMAN: The field is still wide open.

A PHYSICIAN: The patient had diarrhea for two weeks, high fever and a large spleen. The liver increased in size so rapidly, without pain or jaundice, that one might suspect that he had either amebiasis or some other infection that was causing an abscess there.

DR. CHESTER M. JONES: It seems to me that, with an amebic abscess, the patient would have been running a septic temperature.

DR. CASTLEMAN: The chart was flat.

DR. WYMAN RICHARDSON: How about the right half of the diaphragm?

DR. LAURENCE L. ROBBINS: It is normal. About all that these x-ray films do is to confirm the findings of physical examination — an enlarged liver, which extends down over the iliac crest, and a large spleen, which is visible below the costal margin. The only thing that I can add is that there are definitely no varices of the esophagus. The diaphragm is perfectly smooth in outline and shows nothing to suggest lobulation.

DR. RICHARDSON: The bone marrow was normal?

DR. CASTLEMAN: That examination was done at another hospital. We have only the report.

Dr. Jones saw this patient and said: "I am not convinced that cirrhosis is the answer, although it may be. The lack of fever, varices and ascites and the presence of a big liver make me question the diagnosis of cirrhosis of the liver." Have you any further comment, Dr. Jones?

DR. JONES: No, except I think that the first biopsy report of fibrosis and apparent bile-duct proliferation does not prove that that was the picture throughout the liver. I do not believe that it was.

DR. CASTLEMAN: Unless a man is expert at taking a biopsy through a peritoneoscope, he may take a bit of the capsule of the liver, with little underlying tissue, so that the specimen is not a true sample of the liver.

DR. JONES: The specimen may be a thickened capsule with a few bile ducts, and thus does not give an accurate picture. I do not believe that this biopsy makes or breaks the diagnosis. If it were pure cirrhosis, it would tend to be a fatty liver, as Dr. Keefer has pointed out, or biliary cirrhosis. The description given at the second peritoneoscopy — a smooth or finely granular liver with mottled

yellow areas — is not at all unlike what we see in cases of biliary cirrhosis, but it is curious for biliary cirrhosis to show this clinical picture. It does happen, but it is unusual.

DR. CASTLEMAN: How would Dr. Keefer account for the appearance of the liver at the second peritoneoscopy with a diagnosis of cirrhosis and hepatoma? Would they not be easily visible?

DR. KEEFER: That would depend entirely on how far from the surface the hepatoma was. In some hepatomas the original mass is beneath the capsule and does not project beyond the capsule. Although many of them produce large lobulated masses of the liver, a few do not.

DR. RICHARDSON: It would be useful to have detailed information regarding the blood picture. This was a macrocytic anemia. Pernicious anemia could account for it.

DR. CASTLEMAN: I do not believe that the blood picture as reported gave evidence of pernicious anemia.

DR. RICHARDSON: The mean cell volume was 109 cubic microns. I do not know where it was done. If it was done in the Baker Memorial Laboratory that would be on the macrocytic side. Ordinarily it should perhaps be more than that before one could be sure that it was really a macrocytic anemia; 120 cubic microns would be quite suggestive, 109, slightly suggestive.

DR. J. H. MEANS: I suppose it could be lymphoma, although there is no proof of it. He had a large spleen, anemia and fever on one occasion, all of which is suggestive.

CLINICAL DIAGNOSIS

Cirrhosis?
Carcinoma of liver?

DR. KEEFER'S DIAGNOSIS

Cirrhosis of liver, with superimposed bile-duct-cell carcinoma.

ANATOMICAL DIAGNOSIS

Plasma-cell myeloma involving liver and bone marrow.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy of the liver showed no evidence of cirrhosis. The most striking finding was tremendous dilatation of the sinusoids, which were filled with typical plasma cells (Fig. 1). This patient, therefore, had plasma-cell myeloma involving the liver.

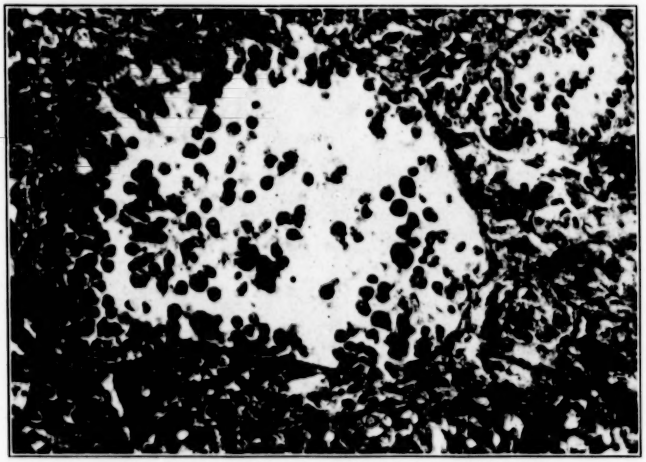

FIGURE 1. *Photomicrograph of the Biopsy Specimen from the Liver.*

To confirm that diagnosis a sternal biopsy was done, and this showed that the marrow was almost completely replaced by plasma cells. When that was confirmed a peripheral blood smear was examined by Dr. Richardson, who found plenty of plasma cells.

The urine was examined and found to contain Bence-Jones protein, which had not been looked for before.

The patient died at home three months later, but no post-mortem examination was performed.

X-ray films were taken after the diagnosis was established.

DR. ROBBINS: There is nothing in the bones to suggest myeloma.

DR. CASTLEMAN: I suppose that the one clue to the diagnosis was the high serum protein.

DR. RICHARDSON: It was not particularly high, but perhaps higher than it should have been.

A PHYSICIAN: How do you account for the fact that the plasma cells were not reported in the bone-marrow biopsy?

DR. CASTLEMAN: We simply had the report from the other hospital.

A PHYSICIAN: Is there a diffuse generalized infiltration, or may it be patchy?

DR. CASTLEMAN: Multiple myeloma is by and large, patchy, as its name indicates, but in the cases in which the bones do not show multiple lesions it is usually a diffuse disease, or what may be called "plasma-cell leukemia." In the patchy type the liver and spleen are almost always normal.

CASE 30252

PRESENTATION OF CASE

First admission. A fifty-nine-year-old Japanese domestic was admitted to the hospital complaining of a tired feeling, anorexia and loss of weight.

About six weeks prior to admission the patient's appetite, which had previously been enormous, became considerably poorer. He began to feel tired. His weight, which had been 178 pounds five years before entry, and 155 four weeks before, was down to 123 pounds on the day of admission. He had been in the United States for forty years and had served as a domestic throughout this period. For twenty years prior to admission he had suffered attacks of epigastric distress, pain and gas, coming on two or three hours after meals and relieved by soda. Five years before entry he had had attacks of vomiting, which ceased after several months. For about six months he had noticed excessive thirst and polyuria. He stated that cirrhosis of the liver had been diagnosed many years previously.

The temperature was 98.6°F., the pulse 76, and the respirations 18. The blood pressure was 210 systolic, 110 diastolic.

Physical examination revealed a thin, cachectic man. The heart was enlarged to the left, and a harsh systolic murmur was heard at the apex. There was slight discomfort on epigastric pressure.

Examination of the blood showed a white-cell count of 7600, with 72 per cent neutrophils, 18 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils. A photometric hemoglobin was 14.3 gm. The urine had a specific gravity of 1.032, and was positive for sugar, but negative for ketone bodies. A gastric analysis revealed 5 units of free hydrochloric acid in the fasting specimen, 53 units thirty minutes after alcohol and 90 units thirty minutes after histamine. The gastric contents and the stool were guaiac negative. A blood sugar was 288 mg. per 100 cc. The blood chloride was 94.9 milliequiv. per liter. A bromsulfalein test revealed less than 15 per cent of dye in the serum at the end of fifteen minutes, and less than 5 per cent after thirty minutes. A phenolsulfonephthalein test was normal.

Roentgenographic examination revealed an ulcer in the prepyloric area; the chest was negative.

After the diabetes had been brought under control with protamine (16-20 units augmented with small doses of regular insulin), a subtotal gastrectomy was performed. The pathology report revealed a chronic active pyloric ulcer on the lesser curvature measuring 2.5 cm. in diameter. There was no evidence of malignant disease. The patient was discharged on the twelfth postoperative day.

Final admission (three and a half months later). At home the patient continued to feel weak and became tired easily. Because of several insulin reactions, even the small doses he had been taking had to be omitted, but his diabetes remained under control. His appetite was poor, and he had epigastric fullness and gaseous eructations after meals. He lost about 10 pounds. About three weeks before readmission he became jaundiced. His urine decreased in amount and became darker in color ten days before admission. His physician palpated a mass in the right upper quadrant, which he thought was the gall bladder.

Physical examination on readmission revealed marked icterus. The liver was enlarged and slightly tender, and a lobular projection, which was also slightly tender, was palpable at its lower border in about the midclavicular line.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed a white-cell count of 8100, with a normal differential count. The hemoglobin was 12 gm. The urine had a specific gravity of 1.006, with a + test for albumin. No sugar or bile was present. The blood sugar was 100 mg. per 100 cc., although the patient was receiving no insulin. The van den Bergh test was 4.2 mg. per 100 cc. direct, and 5.7 mg., indirect. A prothrombin time was 23 seconds (normal, 16 seconds). A Graham test showed that the gall bladder failed to concentrate the dye; no opaque calculi were seen.

On the seventh day the patient's temperature rose to 102°F. and continued to spike from 102 to 104° for seven days. The jaundice became deeper, and two stools were grayish-yellow in color. The chest was clear. The urine gave a +++ test for bile, and a van den Bergh was 12.1 mg. per 100 cc. direct, and 16.8 mg. indirect. On the fifteenth day a cholecystostomy was done, following which the temperature became normal and the icterus diminished. The serum bilirubin dropped to 3.5 mg. per 100 cc. direct, and 4.5 mg. indirect. The red-cell

count was 2,180,000, with 8.3 gm. of hemoglobin. The blood nonprotein nitrogen was 36 mg. and later 26 mg. per 100 cc., and the chloride 88.5 milliequiv. per liter. The blood protein varied from 5.8 to 7.2 gm. per 100 cc., with an albumin-globulin ratio of 0.8. A formol-gel reaction was positive (+ after five minutes, ++ after two hours and ++++ after twenty-four hours). A bromsulfalein test revealed 10 per cent of dye in the serum after twenty-four hours. The urine urobilinogen was normal. A chest film on the eleventh postoperative day was normal.

The patient received two transfusions and numerous intravenous infusions but continued to become weaker. He finally became comatose; the temperature fell to 93.8°F., breathing became very slow, and he finally expired on the twenty-seventh postoperative day.

Differential Diagnosis

Dr. Chester M. Jones: It is apparent from the first few paragraphs of the history that this patient had symptoms of ulcer, proved by x-ray and subsequently by operation. The only discrepancy is the x-ray examination, which implies that the ulcer was in the prepyloric region, but it actually turned out to be at the pylorus, where the incidence of malignant disease is much lower. He had diabetes on the first admission with a high blood sugar and glycosuria. Then there is the statement, which I am not willing to take at face value, that he had had cirrhosis. It is an interesting statement, and I wonder if it is true.

Dr. Benjamin Castleman: Dr. Harwood, do you know whether this patient had had cirrhosis in the past?

Dr. Reed Harwood: His employer stated that the patient had vomited blood and that a diagnosis of cirrhosis had been made, but I think it would be fair for this discussion to say that at the first operation hepatic changes were not seen.

Dr. Jones: I do not believe that there is any reason to say he had cirrhosis on the basis of the story or the findings. Everything is against it, and the hematemesis was probably due to ulcer rather than to esophageal varices. Against the diagnosis of cirrhosis at the time of the first admission are the facts that no liver or spleen was felt, that no x-rays were taken to demonstrate esophageal varices and that he had a dye retention at the end of thirty minutes of only 5 per cent or less. The diagnosis ought to be put in a pigeonhole as a very improbable background against which the rest of this picture is laid. Another variable is the hypertension on admission (systolic 210, diastolic 110), which subsequently disappeared. On the first admission one would be entitled to say that he had hypertension and hypertensive heart changes.

I know nothing about the operative findings. It would be interesting to know about the liver, the gall bladder and the pancreas. In doing a subtotal resection the surgeon should have learned a good deal about these organs. I do not suppose, however, that it is possible to get this information at the moment.

Dr. Castleman: It is not in the operative note.

Dr. Jones: It should have been, but after a difficult operation, where the surgeon's main attention is directed toward a difficult diagnostic problem, the omission can be understood. The operative note should be as full as possible, and in my experience operations with detailed surgical notes are of immense value afterward.

Dr. Castleman: The duodenum in the region of the ulcer was adherent to the pancreas, and no attempt was made to free it.

Dr. Jones: The chances are that the patient did not have gross cirrhosis of the liver or cancer of the pancreas, since the surgeon would have noticed it. This patient had a striking loss of weight during the few months before the first admission, a drop from 155 to 123 pounds in a month. That could have been due to diabetes, and yet it does not seem that the diabetes was quite that severe. Possibly there was some associated disease which at that point had not come to light.

The next series of events came after the operation. He went home for three and a half months, and the diabetes, which may have caused the marked loss of weight and certainly caused increased thirst and polyuria, disappeared from the picture. He had no diabetic symptoms and was having insulin reactions on relatively small doses of insulin. He may have had only a mild diabetes. His appetite was poor after operation, and he had gaseous eructations after meals. After subtotal gastrectomies the majority of patients do extremely well, eat three good-sized meals without symptoms and gain weight rapidly. A fair number, on the other hand, do not have a good appetite and are unable to eat adequately without discomfort, even though their ulcer is cured. Then there is an intermediate group with a long convalescence and slow gain in weight. Three weeks before re-entry he became jaundiced and something new came into the picture that had not been found on careful physical examination three and a half months earlier — a mass that his physician thought was gall bladder. The liver was slightly enlarged and tender, and in addition, a lobular mass was found in the region where the gall bladder could and frequently does lie — the midclavicular line under the hepatic border.

The blood pressure, which had been 210 systolic, 110 diastolic, was 110 systolic, 70 diastolic. That is a rather striking single fact. I cannot explain it, unless it was associated with general loss of weight and of appetite and loss of body tone. It is a curious change.

On readmission we have further evidence that the diabetes was either nonexistent or extremely mild,

and we do not have to pay much attention to it. He was jaundiced. There was one bit of evidence that the gall bladder or biliary tract was diseased in addition to the jaundice, that is, the Graham test showed a nonfilling gall bladder. That could have been due to disease of the gall bladder itself, a stone in the cystic duct, with a fairly normal gall bladder, a block below the cystic duct or intrahepatic disease. He then became definitely febrile and for a week ran a high temperature (100 to 104°F.), with rapidly increasing jaundice and absence of bile from the stools — a picture of extrahepatic biliary obstruction, for which I assume he was operated on fifteen days after admission, only a cholecystostomy having been done. I should say that that was either because he was too poor a risk to do what was desirable or because additional findings precluded further surgery. One does not do a cholecystostomy in a man of fifty-nine these days unless he has a fundamentally inoperable condition. If they thought that he had a block at the ampulla of the common duct that was a permanent affair and could not be removed, they would have chosen to do a cholecystgastrostomy or enterostomy to give relief from the symptoms associated with complete biliary obstruction.

We are not told what the operation showed at that time, but the jaundice diminished and he improved temporarily. At that time the jaundice was on the wane, and he had adequate biliary drainage. The bromsulfalein test, which previously gave less than 5 per cent dye retention, an essentially normal figure, showed 10 per cent of the dye retained in one half hour. That is a minimal amount of dye retention in a patient who was previously jaundiced, and implies little real intrahepatic disease. We know also that some bile was probably coming through into the intestine because the urobilinogen in the urine was normal. There was some leakage of bile. In spite of his temporary improvement he went downhill rapidly and died. His death could perfectly well have been due to nutritional depletion, in the broad sense of the word, or to hepatic failure.

It seems to me that the diagnosis here has to include the probability of malignant disease around the biliary system below the level of the cystic duct. In all probability he had obstructive jaundice that was relieved by a relatively simple operation. He could have had a gallstone in the common duct, but I do not believe that he would have died from an impacted stone in the common duct following cholecystostomy. I also do not believe that he would have developed anemia or would have lost so much weight if it had been a benign condition, such as stone in the common duct. It seems to me that one has to consider the types of blockage that are not strictly benign and that involve the lower end of the common duct or ampulla, and for which one would do a cholecystostomy as a temporary procedure. Cancer of the ampulla could perfectly well have been missed at the first operation. Cancer of the common duct could equally well have been missed. These are both relatively rare conditions but must be considered. Cancer of the gall bladder should not have been missed on the first admission if the surgeon had looked anywhere outside the operative field, and I am sure that he did. Cancer of the pancreas with involvement of the head and subsequent obstructive jaundice must also be considered. Diabetes occurs with cancer of the pancreas, but it is not the usual thing; it is relatively uncommon because there is enough normal islet-cell tissue left to take care of the sugar metabolism. It seems to me that this patient had obstruction of the common duct, and that it was most likely due to a malignant process involving either the ampulla, the common duct or the head of the pancreas. I do not believe that it could have been due to carcinoma that had been missed in the stomach or duodenum and had metastasized. I do not believe that it was a primary hepatoma of the liver. A palpable gall bladder may still be normal, the enlargement being due either to stone in the common duct or to malignant disease. There are times when Courvoisier's law does not work; however, a palpable gall bladder in the presence of painless jaundice usually means obstruction at the lower end of the common duct due to carcinoma. Apparently here we should direct our attention away from the gall bladder, considering it to be the end result of obstruction. I believe that there was an obstructing malignant process around the ampulla.

Could he have had a benign inflammatory process, such as chronic pancreatitis? A short time ago Dr. Arthur W. Allen and I discussed a case[1] here in which that was exactly what had happened: a fibrosis of the pancreas, which gradually involved the region of the ampulla and eventually gave a picture like this, without involvement of the gall bladder itself. But that is extremely rare and not likely in this case.

There is one other thing I should like to mention merely for discussion, that is, the diabetes. He had diabetes and it disappeared. I am assuming, of course, that these statements are correct. It is an interesting phenomenon and has been observed under somewhat similar circumstances. Several years ago Bordley[2] at the Johns Hopkins Hospital wrote an article in which he discussed a case of cirrhosis of the liver in which, as jaundice and cirrhosis developed in a previously known, treated case of severe diabetes, the sugar tolerance returned to normal. I have had one such case, and there are four or five cases reported in the literature, but it is a rare occurrence. With these cases in mind I suppose it is reasonable simply to speculate on the possibility that the diabetes became better because the patient had intrahepatic involvement, a very curious phenomenon.

I shall have to conclude by saying that I am unable to rule out cancer of the pancreas.

DR. HARWOOD: When I first saw this patient he came in for study because of abdominal pain and diabetes. He had severe diabetes, and my recollection is that preoperatively he needed 60 units of insulin. He had never been sugar free before the gastric resection, but immediately following operation his diabetes diminished, and he was discharged on 24 units of protamine insulin. I followed him for the next three months, and he did well on a four-stage gastric diet and had no digestive symptoms. He continued to feel poorly, however, and was never able to do the lightest type of domestic work. He was still weak, and I could not understand why. His blood pressure was 95 systolic, 60 diastolic. I kept wondering if the combination of decrease in need for insulin and of drop in blood pressure was due to adrenal-gland deficiency and kept watching for signs of pigmentation that never developed. He returned to the hospital, but unfortunately we did not get a blood sodium. His jaundice developed at the same time that he began to have gaseous eructations and loss of appetite, and as I remember, there was no pain associated with it.

DR. LELAND S. MCKITTRICK: I have arrived just in time to explore the patient, I take it.

DR. JONES: Yes, and may I ask a question? I made the statement, which I should like to have you comment on, that ordinarily one would have done more than a cholecystostomy for obstructive jaundice, and therefore the explanation is that the patient was too sick to do more or that a condition was found at operation that made it unwise to go farther. Is that reasonable?

DR. MCKITTRICK: Or else that I did not want to burn any bridges.

We were told that he had had cirrhosis over a long period of time. In addition, he had a big palpable gall bladder and he really had an enormously dilated biliary tree, so that, regardless of cirrhosis or anything else, he must have had obstruction of the outlet to the common duct. What it was, or what was back of it all, we knew no more at the completion of the operation than we did at the beginning. The patient was a sick man and was getting sicker, and one of the reasons he was getting sicker was the biliary obstruction. Therefore the obvious thing to do was to relieve the biliary obstruction and do no more, and that is where he was left.

DR. JONES: I am sorry that you were not here to hear a statement that I made. If he had cirrhosis, unless it was a slight biliary cirrhosis, would it not have been easily noticed at the first operation?

DR. MCKITTRICK: When one is presented with a big problem, and one as important as this, it is surprising how blind one may be.

DR. JONES: I suggested that.

DR. MCKITTRICK: It is possible that he had cirrhosis of the liver.

My general concern was eliminating what at that time was thought to be carcinoma of the stomach. The only type he could have had would have been a moderate biliary cirrhosis without jaundice or evidence of biliary obstruction.

CLINICAL DIAGNOSES

Carcinoma of head of pancreas?
Biliary cirrhosis of liver.
Diabetes mellitus.

DR. JONES'S DIAGNOSES

Extrahepatic biliary obstruction, due to malignant disease (probably cancer of ampulla of Vater or of pancreas).
Moderate hepatic changes secondary to biliary obstruction.

ANATOMICAL DIAGNOSES

Carcinoma of head of pancreas.
Biliary obstructive cirrhosis, very early.
Bile nephrosis.
Diabetes mellitus.
Hyalinization of islets of Langerhans.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this man showed a finely granular greenish liver that was not particularly big; we thought at that time that it was an obstructive type of lesion — general bile stasis or perhaps a mild obstructive cirrhosis.

DR. JONES: Of six or eight weeks' duration?

DR. CASTLEMAN: It could have been longer.

The head of the pancreas was firm, and on sectioning it contained areas of yellowish necrosis, which we were not too sure were carcinoma. Most of us thought that they probably were, but there were no firm granular areas such as one usually sees in carcinoma of the head of the pancreas. The microscopic sections, however, showed that it was a primary cancer of the head of the pancreas.

He also had a mild bile nephrosis and an extremely early biliary obstructive cirrhosis.

DR. HARWOOD: Possibly the thing that cured the diabetes was anorexia and the resultant starvation, which used to be the antidiabetic treatment before insulin was discovered.

DR. CASTLEMAN: The pancreas showed marked hyalinization in the islands of Langerhans, which we have seen in about half our diabetic cases.

DR. HARWOOD: Were the adrenal glands normal?

DR. CASTLEMAN: Yes.

REFERENCES

1. Case records of the Massachusetts General Hospital (Case 29311). *New Eng. J. Med.* 229:251-255, 1943.
2. Bordley, J., III. Disappearance of diabetes mellitus during development of cirrhosis of liver. *Bull. Johns Hopkins Hosp.* 47:113-122, 1930.

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BACILLARY DYSENTERY IN THE UNITED STATES

It is generally believed that dysentery is a disease primarily encountered in tropical and subtropical regions. As a matter of fact, epidemic and endemic bacillary dysentery occurs throughout the world, and although less of a public-health problem in the temperate than in the tropical zones, should be constantly kept in mind by all practicing physicians. The subject has recently been reviewed by Weil,[1] and several of its aspects deserve comment.

Bacillary dysentery is caused by a variety of organisms, including *Bacterium shigae*, *B. flexneri* (including a variant, the Newcastle strain), *B. sonnei* and *B. ambiguum* (Schmitz bacillus). Fortunately, the organism causing the most serious type of dysentery, *B. shigae*, is practically unknown in the United States, the etiologic agents in order of frequency being *B. flexneri*, *B. sonnei* and the Newcastle bacillus. The last is more or less limited to the southern states.

Epidemics of dysentery are chiefly confined to institutions or hospitals for the care of patients with mental diseases or of children—in other words, where living quarters are crowded, where faulty habits of personal hygiene frequently exist and where the carrier rates are usually high. On the other hand, the disease occurs endemically throughout the United States. This is evidenced by the fact that in 1933–1937 vital statistics from twenty-one states recorded over 79,000 cases, with a mortality of 17.8 per cent, and since the actual death rate is believed to be about 2 per cent, this means that the total number of cases, reported and unreported, was in the neighborhood of 700,000. The fatal cases occur chiefly in infants and children; in fact, prior to 1910, diarrhea and enteritis were the most frequent cause of death in infants. Although these diseases have subsequently shown a remarkable decline in many sections of the United States, they are still only exceeded by prematurity as a cause of infant deaths in many southern states.

Infection is spread by direct contact with patients or healthy carriers and by food contaminated by such persons or by flies in areas where there are improper facilities for sewage disposal. The importance of the carrier problem is evidenced by the fact that dysentery bacilli have been cultured from 0.1 per cent of healthy persons in institutions in New York City and from 3.8 per cent in Georgia and New Mexico, from 28 per cent of healthy persons in families in which there had been a case of bacillary dysentery, and from 80 per cent of the inmates of a children's institution in which the disease had been present in epidemic form.

Control of the disease is dependent on adequate methods of sanitation and on the proper handling of patients and of carriers. The patient with bacillary dysentery harbors the causative organism in his intestinal tract for varying periods of time: nearly 3 per cent develop a chronic form of the disease, and 80 per cent of all patients yield positive

stool cultures for a month or more after the acute attack.

Of primary importance is full appreciation by the physician that the disease rarely causes the textbook picture of acute bacillary dysentery, general malaise with one or two days of slight fever, with or without loose stools, being the most frequent clinical syndrome. The patient should not be discharged until an appreciable number of negative cultures have been obtained — the British authorities recommend eight negative cultures in four weeks, or six in six weeks. Certain of the sulfonamide drugs, particularly those that are slowly absorbed from the intestinal tract, — such as sulfaguanidine, — have been claimed to be effective in ridding the bowel of the bacilli; in fact, a recent report states that in 208 cases, of which 190 were caused by *B. flexneri* and 18 by *B. sonnei*, that occurred among the armed forces in North Africa the stools were negative in 194 after one course of treatment with sulfaguanidine and those of the remainder became negative after a subsequent course of sulfadiazine.[2] Others have reported less successful results, particularly in cases due to *B. sonnei*, but this method deserves a thorough trial.

The detection of carriers presents a difficult problem. It is obvious that all carriers cannot be discovered, and even the examination of food handlers in institutions, hospitals, hotels, restaurants and the like has proved to be impractical. One of the most effective methods of lowering the incidence of the disease is the enforcement of proper personal-hygiene practices among food handlers.[3]

Although typhoid fever has been practically eradicated in temperate zones, it appears unlikely that the same results can be obtained with bacillary dysentery. On the other hand, there is no doubt that the incidence of the disease can be greatly lowered if proper precautions are observed.

References

1. Weil, A. J. Progress in study of bacillary dysentery. *J. Immunol.* 46:13-46, 1943.
2. Page, S. G., Jr. Sulfaguanidine in treatment of bacillary dysentery. *Bull. U. S. A. Med. Dept.* No. 78, January, 1944.
3. Getting, V. A. Epidemiologic aspects of food-borne disease. *New Eng. J. Med.* 228:754-762, 788-796 and 823-830, 1943.

INJURIES TO THE EYES FROM AIR RIFLES

Injury to the eye from the pellet of an air rifle is an all too frequent injury. Probably there is no time during the year when one cannot find on the wards of one of the Boston eye hospitals a patient whose eye has been injured in this manner. Usually the pellets, although they strike the eye with great force, do not perforate the globe. The violent contusion, however, may lead to the most serious complications. One often sees massive intraocular hemorrhage, dislocation of the lens, cataract, ruptures of the retina and choroid, and detachment of the retina. Seldom does an eye injured in this way escape permanent damage, and often permanent total blindness results.

This is truly preventable blindness. So long as air rifles are allowed to come into the hands of young people these injuries are bound to occur. The world would be no loser if this gun were outlawed. Since, however, there is no control over those who are permitted to use air rifles, every Massachusetts physician should comply with the law that requires the reporting of all such injuries and should conform to the other suggestions that appear in a letter published elsewhere in this issue of the *Journal*.

MASSACHUSETTS MEDICAL SOCIETY

DEATH

DOWNING — Andrew F. Downing, M.D., of Cambridge, died June 2. He was in his sixty-seventh year.

Dr. Downing received his degree from Harvard Medical School in 1904. He was a member of the staffs of the Cambridge City Hospital, Boston Dispensary, St. Elizabeth's Hospital and the Massachusetts General Hospital. He was a member of the American Medical Association and a former president of the Cambridge Medical Improvement Society.

His widow and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN

Clinic	Date	Clinic Consultant
Salem	July 3	Paul W. Hugenberger
Haverhill	July 5	William T. Green
Brockton	July 13	George W. Van Gorder
Pittsfield	July 17	Frank A. Slowick
Worcester	July 21	John W. O'Meara
Fall River	July 24	Eugene A. McCarthy
Hyannis	July 25	Paul L. Norton

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1944

Résumé

Diseases	May 1944	May 1943	Seven-Year Median
Anterior poliomyelitis	1	1	1
Chancroid	3	*	*
Chicken pox	2560	1125	1207
Diphtheria	22	4	11
Dog bite	1421	1136	1259
Dysentery, bacillary	36	12	5
German measles	377	8077	259
Gonorrhea	440	360	358
Lymphogranuloma venereum	4	*	*
Measles	4209	6993	4118
Meningitis, meningococcal	54	74	8
Meningitis, Pfeiffer-bacillus	1	2	2
Meningitis, pneumococcal	3	11	†
Meningitis, staphylococcal	0	0	†
Meningitis, streptococcal	2	1	†
Meningitis, other forms	5	1	†
Meningitis, undetermined	9	23	*
Mumps	1438	645	943
Pneumonia, lobar	292	232	355
Salmonella infections	15	6	20
Scarlet fever	1513	1947	976
Syphilis	439	507	507
Tuberculosis, pulmonary	248	279	285
Tuberculosis, other forms	14	17	23
Typhoid fever	3	1	2
Undulant fever	7	3	3
Whooping cough	324	537	757

*Made reportable in December, 1943.

†Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

Comment

Chicken pox continues at a high level. The seasonal decline is also slow this year.

Diphtheria continues at a fairly high level as compared with last year. The figure for May is exactly twice the seven-year median.

Bacillary dysentery figures are high but most of the cases occurred in a large state hospital.

This is the third successive month in which meningococcal meningitis has been lower than in the corresponding month in 1943.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Newton, 1; total, 1.

Diphtheria was reported from: Belmont, 1; Boston, 4; Fairhaven, 1; Fall River, 1; Haverhill, 2; Lawrence, 3; Medford, 1; Melrose, 1; Somerville, 6; West Newbury, 1; Winthrop, 1; total, 22.

Dysentery, bacillary, was reported from: Boston, 1; Chicopee, 2; East Bridgewater, 1; Newton, 1; Worcester (State Hospital), 31; total, 36.

Encephalitis, infectious, was reported from: Billerica, 1; Worcester, 1; total, 2.

Malaria was reported from: Andover, 1; Boston, 2; Brookline, 2; Cambridge, 4; Camp Edwards, 7; Concord, 1; Cushing General Hospital, 9; Fort Banks, 10; Fort Devens, 19; Hanson, 1; Haverhill, 3; Holbrook, 2; Holyoke, 1; Medford, 5; Revere, 1; Salem, 1; Somerville, 3; U. S. Marine Hospital, Boston, 1; Wakefield, 3; Waltham, 1; Wareham, 1; Weymouth, 1; Woburn, 2; Worcester, 1; total, 82.

Meningitis, meningococcal, was reported from: Amherst, 1; Attleboro, 1; Boston, 19; Brockton, 1; Brookfield, 1; Cambridge, 2; Chelsea, 1; Easton, 1; Everett, 1; Fall River, 1; Fitchburg, 1; Hingham, 1; Lawrence, 2; Lexington, 2; Lowell, 1; Malden, 1; Millville, 1; Needham, 1; Newton, 1; North Attleboro, 1; Oxford, 1; Quincy, 2; Reading, 1; Salem, 1; Seekonk, 1; Somerville, 3; Springfield, 2; U. S. Marine Hospital, 1; Winthrop, 1; total, 54.

Meningitis, Pfeiffer-bacillus, was reported from: Monson, 1; total, 1.

Meningitis, pneumococcal, was reported from: Brockton, 1; Easthampton, 1; Ware, 1; total, 3.

Meningitis, streptococcal, was reported from: New Bedford, 2; total, 2.

Meningitis, other forms, was reported from: Boston, 4; Lynn, 1; total, 5.

Meningitis, undetermined, was reported from: Hingham, 2; Needham, 1; New Bedford, 1; Quincy, 1; Southbridge, 1; Springfield, 1; Weymouth, 1; Worcester, 1; total, 9.

Salmonella infections were reported from: Gardner, 1; Holden, 1; Malden, 2; Manchester, 3; Melrose, 1; Springfield, 1; Wellesley, 2; Worcester, 4; total, 15.

Septic sore throat was reported from: Boston, 10; Carver, 1; Everett, 1; Haverhill, 3; Hingham, 2; Lowell, 1; Malden, 1; Mansfield, 1; Quincy, 1; Winchester, 1; total, 22.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Attleboro, 1; Brockton, 1; Newton, 1; total, 3.

Undulant fever was reported from: Boston, 1; Bridgewater, 1; Danvers, 1; Egremont, 1; Fitchburg, 1; Great Barrington, 1; Shelburne, 1; total, 7.

CORRESPONDENCE

INJURIES TO THE EYES FROM AIR RIFLES

To the Editor: Since the start of the war there has been an alarming increase in the number of eyes seriously injured by BB guns. This is not surprising when one stops to note that children of all ages are war conscious, as evidenced by the preponderance of toys fashioned in military motives. The present law, a copy of which is appended, requires that all air-rifle injuries be reported to the Commissioner of Public Safety and to the police, regardless of the triviality of the wound.

The Massachusetts Division of the Blind is extremely anxious to get statistics on all BB-gun injuries. Its program of prevention of blindness can make no concession with the use of these dangerous toys by children, and it is exerting every effort to make illegal the sale of this weapon. Most of these injuries occur in children under sixteen years of age, and oftener than not, it is an innocent person who is the victim. The time to act is before an accident occurs. The non-magnetic character of the pellet makes for a poor prognosis in the eye, although it may do no serious damage elsewhere in the body. For the sake of many potential victims every physician in the Commonwealth is urged to:

Comply with the law requiring that all BB-gun injuries be reported to the Commissioner of Public Safety and to the local police department.

Drop a card to the Massachusetts Division of the Blind, 110 Tremont Street, Boston, stating that a case has been treated (regardless of what part of the body was struck).

Spread the word of the dangers of BB guns to all patients.

Arthur F. Sullivan, *Director*
Division of the Blind

110 Tremont Street
Boston

* * *

Chapter 112

Section 12A. Every physician attending or treating a case of bullet wound, gunshot wound, powder burn or any other injury arising from or caused by the discharge of a gun, pistol, BB gun, or other air rifle or other firearm, or, whenever any such case is treated in a hospital, sanitarium or other institution, the manager, superintendent or other person in charge thereof, shall report such case at once to the commissioner of public safety and to the police authorities of the town where such physician, hospital, sanitarium or institution is located. . . .

DEPRIVATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Louis L. Hoff, Holyoke, Massachusetts, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

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